1-PROPARGYLBENZOTRIAZOLE -- A USEFUL BUILDING BLOCK IN THE SYNTHESES OF HETEROCYCLES

BY

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To my wife, Linghong, and my daughter, Stephanie,

with love

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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August, 1995

Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

1-Propargylbenzotriazole, readily prepared from benzotriazole and propargyl bromide, has been used as a synthetic building block in [3 + 2] annulations either as a two-carbon unit or a three-carbon unit for the synthesis of various 5-membered heterocycles. The benzotriazolylmethyl side chains attached to heterocycles are produced and further elaborated by alkylation and substitution.

1-Propargylbenzotriazole undergoes lithiation first at the acetylenic CH and then at the CH_2 group. The dilithiated species, generated by treatment of 1-propargylbenzotriazole with two equivalents of butyllithium, reacts with an electrophile first at the carbon atom adjacent to the nitrogen, and then at the terminal carbon. Hence lithiation of 1-propargylbenzotriazole and subsequent reactions with electrophiles afford mono- and di-alkylated products depending upon the amounts of butyllithium and of the electrophiles used.

Base-assisted cyclizations of 1-[3-hydroxy(substituted-methyl)propargyl]-benzotriazoles, derived from lithiated 1-propargylbenzotriazole and aromatic

aldehydes or ketones, give 2-arylfurans or 1-(5,5-diaryl-2,5-dihydrofuran-2-yl)benzotriazoles, respectively. The reactions of 1-(5,5-diaryl-2,5-dihydrofuran-2-yl)-benzotriazoles with Grignard reagents yield trisubstituted 2,5-dihydrofurans.

Reactions of 1-(3-lithiopropargyl)benzotriazole with *N*-tosylarylimines give adducts which undergo cycloelimination on treatment with ethanolic alkali to afford 2-aryl- and 2-hetaryl-pyrroles. Treatment of 1-(1,3-dilithiopropargyl)benzotriazole successively with one equivalent of an alkyl halide followed by *N*-tosyl-(1-naphthyl)-imine and then ethanolic alkali gives the corresponding 5-alkyl-2-(1-naphthyl)-pyrroles.

The 4-Substituted and 4,5-disubstituted 2-(benzotriazol-1-yl)methylfurans have been prepared from 1-propargylbenzotriazole and α-bromoketones *via* one-pot processes. The 2-(benzotriazol-1-yl)methyl side chains are alkylated by lithiation followed by quenching with electrophiles to afford 4- and 4,5-substituted 2-(α-benzotriazol-1-yl)alkylfurans. Substitutions of benzotriazolyl groups with other heterocycles in the presence of $ZnCl_2$ give a variety of 4- and 4,5-substituted 2-(α-heterocyclo)alkylfurans.

Replacement of the benzotriazole moiety of *N*-alkyl-2-(1-benzotriazol-1-yl-alkyl)indoles, prepared from 1-propargylbenzotriazole and *o*-iodoaniline followed by alkylation, with Grignard reagents gives the corresponding 2-substituted indoles. Treatment of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indoles with zinc chloride afforded 6,12-disubstituted-6,12-dihydroindolo[3,2-b]carbazoles. The 6,12-Disubstituted-5,11-dihydroindolo[3,2-b]carbazoles are prepared readily from 2-(benzotriazol-1-yl-alkyl)indoles *via* dimerization in the presence of zinc chloride followed by dehydrogenation on exposure to air.

The 4-Substituted- and 4,5-disubstituted-2-(benzotriazol-1-yl)methylpyrroles are easily prepared from the reaction of 5-(benzotriazol-1-yl)-1,2-epoxy-3-pentyne derivatives and primary amines in *i*-PrOH. The 2-(benzotriazol-1-yl)methyl side chains are elaborated by nucleophilic substitution and also by initial alkylation followed by replacement or elimination of benzotriazolyl moiety to afford a variety of 2,4-di- and 2,3,5-trisubstituted-pyrroles.

CHAPTER I
GENERAL INTRODUCTION

The propargyl moiety is one of the most important carbon functional groups in synthetic organic chemistry because of its availability and the great versatility of its transformations. Much of the interest in the use of propargyl units involves (i) inter- and intra-molecular additions to the triple bond, which frequently result in specifically substituted acyclic and cyclic alkenes; (ii) base-assisted rearrangement of propargyl to allenyl, which is also a versatile species; (iii) metalations due to the acidity of the alkynyl and methylene protons and subsequent alkylations or coupling reactions of alkynyl and methylene carbons with a wide range of electrophiles, which are especially attractive and have been widely employed in carbon chain extension reactions recently. The great value of the propargyl group in organic synthesis and the synthetic applications of propargyl derivatives have been well and frequently documented [78MI199, 91MI81, 94MI1 and 95OPP127].

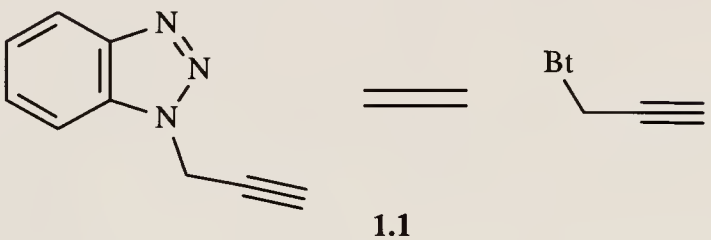
Over the last several years, the use of benzotriazole as synthetic auxiliary in the preparation of many useful organic compounds has been intensively investigated in the Katritzky research laboratory [91T2683, 94S445 and 94MI31]. Due to the electron-withdrawing nature of the nitrogen-nitrogen double bond, benzotriazole possesses two important features: (i) the ability to act as an activating group towards α-proton loss and (ii) good leaving ability in the nucleophilic substitutions.

Combination of the propargyl and benzotriazolyl moieties generates an interesting synthetic precursor, 1-propargylbenzotriazole (**1.1**), with which a variety

of synthetic transformations can be realized.

First, both the sp^3-CH_2 and the sp-CH can be lithiated, and regioselective reactions of the corresponding mono- and di-anions can be directed to occur with electrophiles on either the sp- or sp^3-hybridized carbon atom or at both of these centers.

1-PROPARGYLBENZOTRIAZOLE



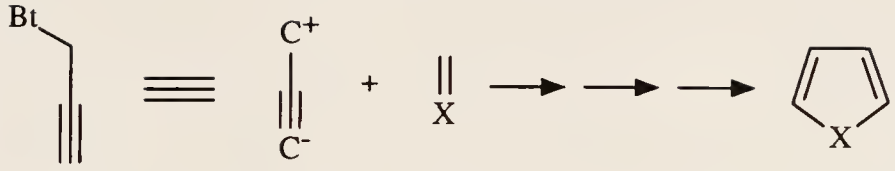
1.1

Secondly, and most importantly, 1-propargylbenzotriazole (**1.1**) can serve as a synthetic building block in [3 + 2] annulations for the syntheses of 5-membered heterocycles. As shown in the following schemes, 1-propargylbenzotriazole (**1.1**) can behave as the 1,3-dipolar species **1.2** which can form rings with carbonyl groups or imines **1.3** to afford furans or pyrroles **1.4**. On the other hand, the triple bond of **1.1** can also act as a two carbon unit in [3 + 2] annulation with other 1,3-dipolar species **1.5** to provide the benzotriazolylmethyl attached heterocycles of type **1.6**.

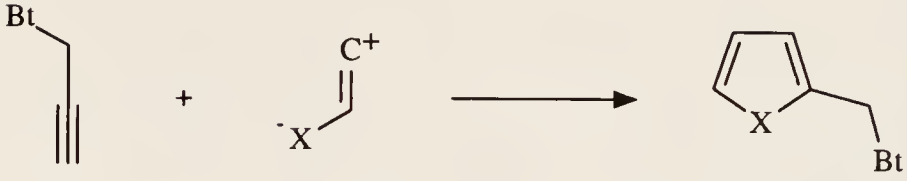
Furthemore, since benzotriazole is both an electron-withdrawing and a leaving group, the benzotriazolylmethyl side chain of **1.6** can be elaborated by lithiation/alkylation and subsequent replacement of the benzotriazole group with nucleophiles.

The objective of this research project was to investigate the applications of 1-propargylbenzotriazole (**1.1**) in the synthesis of a variety of heterocycles. The

[3 + 2] ANNULATIONS

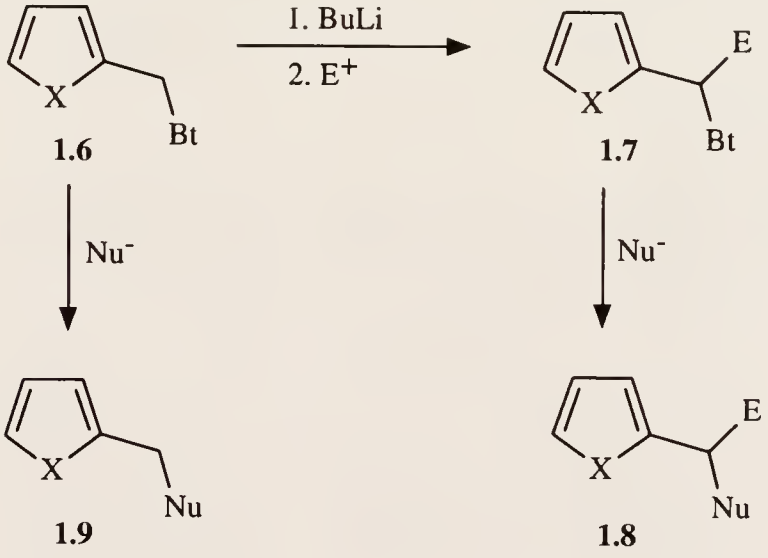


1.1 **1.2** **1.3** **1.4**



1.1 **1.5** X = O, NR **1.6**

ELABORATION OF BENZOTRIAZOLYLMETHYL SIDE CHAIN



1.6 **1.7** **1.9** **1.8**

results will be reported in the following six chapters: Chapter II describes the preparation of 1-propargylbenzotriazole (**1.1**) and the reactions of its lithium derivatives. Chapters III and IV deal with synthetic applications of 1-propargyl-benzotriazole (**1.1**) in the synthesis of substituted furans, dihydrofurans and pyrroles. Chapters V through VII cover the synthesis of 2-(benzotriazol-1-yl)methyl-furans, -indoles and -pyrroles, and the elaborations of their benzotriazolylmethyl side chains.

CHAPTER II
1-PROPARGYLBENZOTRIAZOLE: REACTIONS OF ITS LITHIUM DERIVATIVES

1.1 Introduction

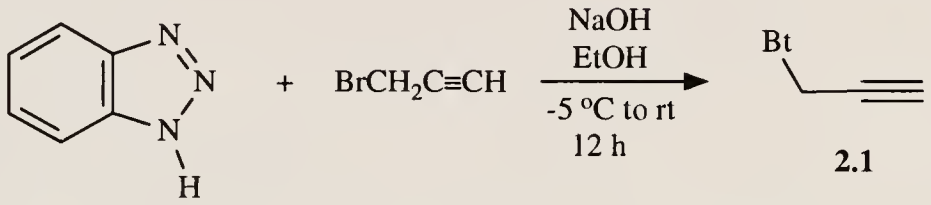
Recently, a large number of benzotriazole derivatives have been prepared in our laboratory and have been used as synthetic precursors for the synthesis of a wide spectrum of useful organic compounds [91T2683, 94S445 and 94MI31]. 1-Propargylbenzotriazole (**2.1**) containing two functional groups, propargyl and benzotriazol-1-yl, should show interesting reactivities, however, it had not been synthesized previously.

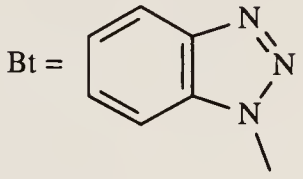
In this chapter, we report the preparation of 1-propargylbenzotriazole (**2.1**) and the reactions of its lithium derivatives.

2.2 Results and Discussion

Since benzotriazole is an electron-withdrawing group, the proton α to the benzotriazole group is relatively acidic and can be deprotonated. However, the acidity of an sp-CH is usually stronger than that of an sp^3-CH, therefore benzotriazoles carrying acetylene groups could show interesting behavior on lithiation. 1-Propargylbenzotriazole (**2.1**) was prepared in 60% yield from benzotriazole and propargyl bromide in the presence of sodium hydroxide at room temperature (Scheme 2.1). When the ^{1}H- and ^{13}C-NMR spectra of the crude product were examined (see

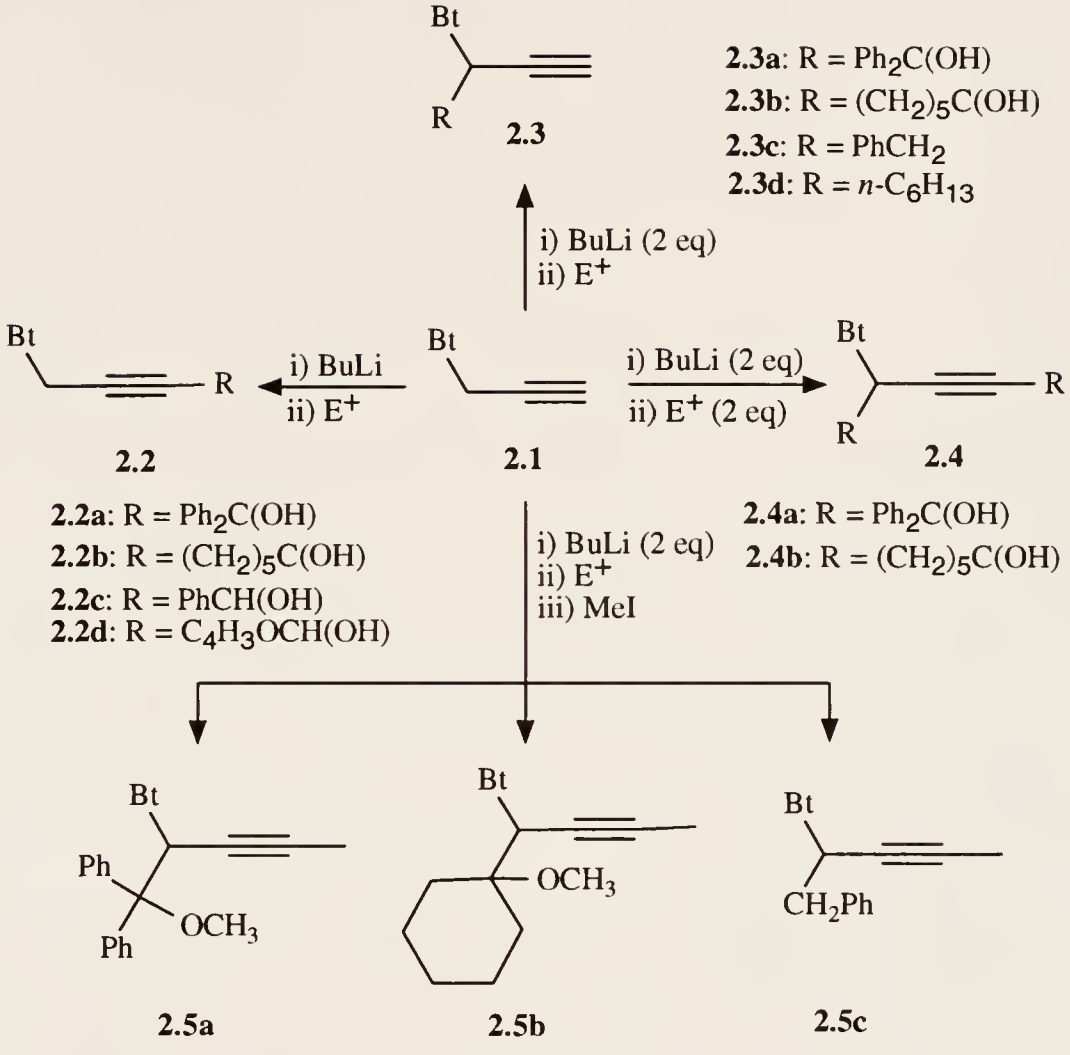
Experimental), the presence of about 30% of 2-allenylbenzotriazole besides the major product 1-propargylbenzotriazole (**2.1**) was demonstrated. Presumably 2-propargylbenzotriazole initially formed is easily isomerized into the allenyl isomer. The 1-propargylbenzotriazole (**2.1**) was purified by crystallization twice from diethyl ether/hexane.





Scheme 2.1

1-Propargylbenzotriazole (**2.1**) on lithiation with one equivalent of butyllithium in THF followed by reaction with benzophenone gave compound **2.2a** in 60% yield. Likewise, compounds **2.2b-d** were obtained in 60-70% yields from cyclohexanone, benzaldehyde and furfural respectively (Scheme 2.2). The ^{1}H-NMR spectra of compounds **2.2b-d** show clearly that mono-lithiation occurs at the acetylenic hydrogen, the CH_2 protons adjacent to the benzotriazole nitrogen (singlets at δ = 5.42-5.92) remain unchanged compared with the starting material whereas the acetylenic proton (at δ = 2.16-2.70) disappears in the ^{1}H NMR spectra. These deductions were confirmed by the attached proton test (APT) in the ^{13}C NMR spectra. The structures of compounds **2.2a-d** were also supported by their elemental analyses (Table 2.1).



Scheme 2.2

On the other hand, when 1-propargylbenzotriazole (**2.1**) was lithiated with two equivalents of butyllithium and quenched with one equivalent of benzophenone, the monosubstituted compound **2.3a** was formed in 67% yield. Similar procedures with cyclohexanone, benzyl bromide and hexyl iodide produced compounds **2.3b-d** respectively in 67-81% yields (Table 2.1). In these cases, the electrophilic substitutions occur at the carbon atom adjacent to the benzotriazole nitrogen rather than at the acetylenic carbon (Scheme 2.2). The structures of compounds **2.3a-d** were

easily deduced from their analyses, and ^{1}H and ^{13}C NMR spectra (Tables 2.1 to 2.3).

These results demonstrate that if one equivalent of butyllthium is used, the more acidic acetylenic proton is removed and the subsequent alkylation occurs at the acetylenic position to form compounds **2.2**. When two equivalents of butyllithium are used, a 1,3-dilithiated derivative of **2.1** is obviously produced and if only one equivalent of electrophile is added, the more basic carbanion adjacent to benzotriazole nitrogen reacts to form compounds **2.3**.

If the above reasoning is correct, using two equivalents of butyllithium and two equivalents of electrophile should form dialkylated products. When **2.1** was lithiated with two equivalents of butyllithium and the resulting 1.3-dilithiated derivative was treated with two equivalents of benzophenone, the dialkylated product **2.4a** was indeed obtained in 54% yield. Similar treatment with cyclohexanone gave compound **2.4b** in 79% yield. The bisalkylated products **2.4a** and **2.4b** were characterized by their elemental analyses and NMR spectral data. No acetylenic proton signal was seen in the ^{1}H NMR spectra and the one-proton singlet at δ = 6.68 (**2.4a**) and 5.76 (**2.4b**) was assigned to the CH group adjacent to the benzotriazole nitrogen.

According to these results, quenching the di-lithiated intermediate successively with one equivalent of one electrophile followed by a different electrophile should result in the corresponding unsymmetrically disubstituted product. Thus, **2.1** was treated with two equivalents of butyllithium followed by one equivalent of benzophenone and then an excess of methyl iodode to give the product **2.5a** in 69% yield. Similar initial reaction with cyclohexanone followed by methyl iodide gave compound **2.5b** (49%). Because of the presence of excess methyl iodide, the hydroxy groups in the initially formed products were also methylated, as was indicated by the

methoxy signals in the ^1H NMR (δ = 3.18 for **2.5a** and δ = 3.26 for **2.5b**) and the ^{13}C NMR spectra (δ = 51.7 for **1.5a** and δ = 49.3 for **2.5b**). When benzyl bromide was used as the first electrophile in a similar procedure, the mixed bisalkylated product **2.5c** was formed in 51% yield. As previously discussed, the first electrophile would attack the more nucleophilic carbanion position adjacent to the benzotriazole, and methyl iodide would then react with the acetylenic carbanion to form the bisalkylated product **2.5** as shown in scheme 2.2. This was supported by the AX_2-spin pattern (a triplet at δ = 5.92 and a doublet at δ = 3.46) assigned for $CHCH_2Ph$ in the ^1H NMR spectrum of **2.5c.**

2.3 Experimental

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded with a Varian VXR 300 FT mode NMR spectrometer, operating at 300 MHz for ^1H and 75 MHz for ^{13}C NMR. The chemical shifts of the proton-NMR spectra are reported in δ values downfield from tetramethylsilane (TMS) as internal standard and the chemical shifts of ^{13}C NMRs are reported in δ values using a deuterated solvent ($CDCl_3$ or $[D_6]$DMSO as the internal standard). -Abbreviation: Bt = benzotriazole. -Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plastic sheets (E. Merck Co.). Column chromatography was conducted over silica gel (200-400 mesh). -Tetrahydrofuran was predried over 4-Å molecular sieves and distilled from sodium/benzophenone under nitrogen. Electrophiles were purified by standard methods before use. Lithiations were carried out in oven-dried (130°C) Schlenck reactors under argon or nitrogen.

2.3.1 Preparation of 1-Propargylbenzotriazole (**2.1**)

A solution of sodium hydroxide (10.0 g, 0.25 mol) in water (25 ml) was added slowly, with vigorous stirring, to an ice-cold solution of benzotriazole (29.75 g, 0.25 mol) in absolute ethanol (150 ml). After 10 min, propargyl bromide (35.9 g, 0.275 mol, 80% in hexane) was added, the mixture was allowed to warm to room temperature. Et_2O (200 ml) and H_2O were added and the organic phase was separated, washed with H_2O and dried ($MgSO_4$). Removal of the solvent gave an oil which was recrystallized from Et_2O/hexane to afford 1-propargylbenzotriazole (**2.1**) (23.6 g, 60%); m.p. 57-58°C. -^{1}H NMR: δ = 8.06 (1H, d, *J* = 8.4 Hz, Ar-H), 7.36-7.72 (3H, m, Ar-H), 5.44 (2H, s, CH_2), 2.51 (1H, s, CH). -^{13}C NMR: δ = 109.7, 120.0, 124.0, 127.6, 132.3, 146.1 (Ar-C), 75.2 (-C≡), 75.0 (≡CH), 37.9 (CH_2). $C_9H_7N_3$ (157.2). Calcd. C, 68.78, H, 4.49, N, 26,73. Found. C, 68.98, H, 4.45, N, 27.02.

The second component, 2-allenylbenzotriazole, could not be isolated in pure form but the ^{1}H NMR spectra of the mixture show signals for 2-allenylbenzotriazole at δ = 7.82-7.85 (2H, m, H-Bt), 7.33-7.38 (2H, m, H-Bt, overlapped by 1-propargylbenzotriazole signals), and the ^{13}C NMR spectra showed signals at δ = 117.6. 126.8, 144.7 (C-Bt), 203.9 (=C=), 103.1 (CH_2) and 88.9 (CH). The chemical shift of allene carbon fall within the range of δ = 211.4 [72JA5084]. These spectral data comfirmed the presence of 2-allenylbenzotriazole.

2.3.2 General Procedure for Lithiation of 1-Propargylbenzotriazole (**2.1**)

To a stirred solution of **1.1** (5 mmol) in THF (50 ml) was added a solution of butyllithium (2.2 ml, 2.5 M in cyclohexane for **2.2a-d** or 4.4 ml, 2.5 M in cyclohexane

for **2.3a-d, 2.4a-b** and **2.5a-c**), dropwise, at -78°C. The mixture was stirred at this temperature for 45 min. A solution of the alkyl halide or ketone (5 mmol for **2.2a-d** and **2.3a-d**, 10 mmol for **2.4a-b**) in THF (5 ml) was added (for **2.5a-c** first 5 mmol of ketone or halide was added followed by 10 mmol of iodide). The mixture was allowed to warm to room temperature and then stirred for 2h. The reaction was quenched with water, the product extracted with diethyl ether (3 x 100 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to give ayellow oil. This was purified by column chromatography or recrystallization (Table 2.1).

Table **2.1** Alkylation of 1-Propargylbenzotriazole (**2.1**)

compd. No.	yield (%)	m.p. (^{o}C)	Crystal form	molecular fomula	analysis / HR-MS found (%)			required (%)		
					C	H	N	C	H	N
2.2a	64	198-9	powder	$C_{22}H_{17}N_3O$	77.79	4.99	12.39	77.86	5.05	12.38
2.2b	70	150-1	cubes	$C_{15}H_{17}N_3O$	70.30	6.80	16.28	70.30	6.71	16.46
2.2c	68	97-8	cubes	$C_{16}H_{13}N_3O$	72.47	4.87	15.82	72.99	4.98	15.96
2.2d	63	--	oil	$C_{14}H_{11}N_3O_2$		253.0843			253.0851	
2.3a	67	179-80	powder	$C_{22}H_{17}N_3O$	77.64	5.03	12.23	77.86	5.05	12.38
2.3b	81	97-8	cubes	$C_{15}H_{17}H_3O$	71.66	7.55	14.83	77.06	7.47	14.83
2.3c	67	--	oil	$C_{16}H_{13}N_3$		247.1114			247.1109	
2.3d	78	--	oil	$C_{15}H_{19}N_3$		241.1574			241.1579	
2.4a	79	186-7	powder	$C_{35}H_{27}N_3O_2$	80.27	5.20	7.97	80.44	5.40	8.04
2.4b	54	--	oil	$C_{21}H_{27}N_3O_2$		353.2090			353.2103	
2.5a	69	--	oil	$C_{24}H_{21}N_3O$		367.1678			367.1685	
2.5b	49	113-4	powder	$C_{17}H_{21}N_3O$	70.97	6.70	16.43	70.56	6.71	16.41
2.5c	51	--	oil	$C_{17}H_{15}N_3$		261.1265			261.1266	

Table **2.2** ^{1}H NMR Data of Lithiation Products **2.2-2.5**

compd. No.	benzotriazole-H	$BtCH_2$	BtCHR	≡CH	OCH_3	CH_3	R
2.2a	8.09(1H, d, *J*=8.4), 7.98(1H, d, *J*=8.1) 7.60(1H, t , *J*=8.1), 7.45(1H, t, *J*=8.4)	5.92	--	--	--	--	7.55-7.45(m, 4H), 7.33-7.20(m, 6H) 6.86(s, 1H, OH)
2.2b	8.06(1H, d, *J*=8.4), 7.70(1H. d, *J*=8.0) 7.51(1H, t, *J*=8.0), 7.38(1H, t, *J*=8.4)	5.49	--	--	--	--	2.40(br, 1H, OH), 1.85(m, 2H), 1.70 -1.40(m, 8H)
2.2c	7.97(1H, d, *J*=8.4), 7.63(1H, d, *J*=8.4) a	5.56	--	--	--	--	7.50-7.40(m,3H), 7.35-7.30(m, 4H) 5.50(s, 1H, CH), 3.40(br, 1H, OH), a
2.2d	7.91(1H, d, *J*=8.4), 7.64(1H, d, *J*=8.4) 7.39(1H, t, *J*=8.1). 7.30(1H, t, *J*=8.4)	5.44	--	--	--	--	7.32(1H, d, *J*=0.9), 6.32(1H, d, *J*=0.7) 6.25(m, 1H), 5.53(s, 1H, CH), 5.05(s, 1H)
2.3a	7.93(1H, d, *J*=8.4), 7.70(1H, d, *J*=8.0) a	--	6.72(d, *J*=2.4)	2,58(d, *J*=2.4)	--	--	7.68(2H, d, *J*=7.8), 7.45-7.30(m, 5H), 7.18(m, 2H), 7.05(m, 3H), 4.18(s, 1H), a
2.3b	8.01(1H, d, *J*=8.4), 7.93(1H, d, *J*=8.4) 7.46(1H, t, *J*=8.1), 7.34(1H, t, *J*=8.1)	--	5.75(d, *J*=2.6)	2.70(d, *J*=2.6)	--	--	2.53(br, 1H, OH), 2.00(m, 1H), 1.80-1.40 (m, 7H), 1.15(m, 2H)\
2.3c	8.03(1H, d, *J*=8.4), 7.59(1H, d, *J*=8.1) 7.41(1H,, m), 7.32(1H, t, *J*=8.4)	--	5.79(td, *J*=7.4 and 2.5)	2.64(d, *J*=2.5)	--	--	7.18(m, 3H), 7.03(m, 2H), 2.50(d, *J*=7.2, CH_2)
2.3d	8.08(1H, d, *J*=8.4), 7.80(1H, d, *J*=8.4) 7.50(1H, t, *J*=8.3). 7.39(1H, t, *J*=8.4)	--	5.79(td, *J*=7.6 and 2.4)	2.61(d, *J*=2.4)	--	--	2.25(m, 2H), 1.45-1.20(m, 8H) 0.85(3H, t, CH_3)
2.4a	8.04(1H, m), a	--	6.68(s)	--	--	--	7.90(d, 2H), 7.48-7.09(m, 21H, 6.60(s, OH), 3.35(s,1H, OH), a
2.4b	8.02(1H, d, *J*=8.4), 7.95(1H, d, *J*=8.4) 7.38(1H, t, *J*=8.4), 7.28(1H, m)	--	5.76(s)	--	--	--	4.85(br, Oh), 3.90(br, OH), 2.00(m, 2H) 1.75-1.35(m, 18H)
2.5a	7.92(1H, d, *J*=7.8), a	--	6.33(d, *J*=7.8)	--	3.18	1.80	7.50(m, 2H), 7.40-6.90(m, 11H), a
2.5b	7.94(1H, d, *J*=8.4), 7.80(1H. d, *J*=8.4) 7.35(1H, t, *J*=8.3), 7.25(1H, t, *J*=8.4)	--	5.88(s)	--	3.26	1.83	1.83-1.69(m, 11H)
2.5c	8.03(1H, d, *J*=8.4), 7.61(1H, d, *J*=8.3) a	--	5.92(t)	--	--	1.87	7.20(m, 4H), 7.03(m, 3H), 3.46(2H, d, *J*=7.2), a

[a]Signals of benzotriazole protons are obscured by those of the aromatic protons.

Table **2.3.**. ^{13}C NMR Data of Lithiation Products **2.2-2.5**

compd.	Benzotriazole-C	$BtCH_2$	BtCHR	≡C	OCH_3	CH_3	R
2.2a	110.8, 119.2, 124.3, 127.2, 132.4, 145.3	37.8	--	89.2, 79.2	--	--	72.8(COH), 125.6, 127.5, 127.9, 145.8
2.2b	109.9, 120.0, 124.1, 127.5, 132.4, 146.2	38.5	--	90.6, 75.5	--	--	68.5(COH), 23.0, 25.0, 38.5, 39.6
2.2c	109.9, 119.8, 124.2, 127.6, 132.3, 145.9	38.4	--	86.8, 77.8	--	--	64.2(COH), 126.5, 128.4, 128.6, 139.9
2.2d	110.2, 119.4, 124.1, 127.5, 132.1, 145.4	38.2	--	84.4, 76.7	--	--	57.4(COH), 107.5, 109.8, 142.5, 152.3
2.3a	111.5, 119.8, 123.9, 128.0, 132.9, 142.9	--	59.8	86.5, 81.4	--	--	77.9(COH). 125.6, 126.6, 127.6, 128.4 141.8
2.3b	112.4, 119.6, 123.9, 127.3, 132.8, 146.0	--	61.4	76.5, 74.9	--	--	21.3, 21.4, 25.2, 33.7, 34.7, 34.7(COH)
2.3c	110.3, 119.9, 123.8, 127.2, 131.9, 146.1	--	52.9	78.3, 75.9	--	--	41.9(CH_2), 127.3, 128.4, 129.1, 134.9
2.3d	110.6, 120.2, 124.0, 127.2, 131.6, 146.5	--	51.8	79.0, 75.0	--	--	13.9, 22.4, 25.7, 28.3, 31.4, 35.7
2.4a	114.1, 118.5, 123.6, 127.2, 133.2, 145.9	--	60.5	91.0, 80.1	--	--	72.9, 81.7, 125.5, 125.7, 126.1, 126.4 126.8, 126.9, 143.2, 144.4, 145.0, 145.6
2.4b	112.9, 119.3, 123.9, 127.0, 132.9, 145.7	--	62.0	92.6, 76.3	--	--	21.4, 23.1, 24.9, 25.2, 33.6, 34.7, 39.5 68.5, 75.1
2.5a	111.7, 122.9, 125.9, 127.0, 133.0, 145.4	--	57.4	87.5, 85.4	51.7	3.5	72.4(COH), 127.7, 128.0, 129.2, 139.6
2.5b	112.4, 119.6, 123.4, 126.7, 133.3, 146.2	--	57.8	84.6, 78.7	49.3	3.6	21.5, 25.0, 30.4, 72.1(COH)
2.5c	111.0, 120.3, 124.2, 127.4, 132.4, 146.6	--	54.0	84.4, 74.6	--	3.8	24.9(CH_2), 127.5, 128.8, 129.6, 129.6 136.0

CHAPTER III
NEW SYNTHETIC ROUTES TO FURANS AND DIHYDROFURANS FROM 1-PROPARGYLBENZOTRIAZOLE

3.1 Introduction

Furans constitute one of the most important classes of heteroaromatic compounds. The furan ring is common to many naturally occurring compounds, such as terpenoids, lipids, steroids, ionophores, and aflatoxines [84MI705, 81MI263]. The role of furans and their hydrogenated derivatives is also significant because of the presence of the furan nucleus in the structures of a variety of commmercially important pharmaceuticals, and flavor and fragrance compounds [84MI705, 84JA440], as well as in diverse synthetic intermediates [86CR785]. Numerous synthetic approaches to furans and dihydrofurans are known (for recently reported procedures see 84JA4407, 84JCS(C)804, 85JA7233, 90JA8985, 90JA8995, 91JA8995, 91JOC2955, 91JOC4598, 91TL4687 and references therein), but the most important methods all involve C-O bond formation at the key step of the heterocyclic ring construction.

Recently, efficient [3+2] annulations of allenylsilanes with aldehydes in the presence of $TiCl_4$ [85JA7233], of allenylsilanes with acylium ions [84JA4407], and of the dienolate anion of ethyl 2-bromo-4-[(tert-butyldimethylsilyl)oxy]crotonate with aldehydes [91JOC4598] have been described for the synthesis of substituted furans [84JA4407] and 2,3-dihydrofurans [85JA7233 and 91JOC4598]. These methods, however, are limited by the relatively low availability of the starting compounds:

thus, 2-bromo-4-[(tert-butyldimethylsilyl)oxy]crotonate has been synthesized in three steps from ethyl 4-hydroxycrotonate, tert-butyldimethysilyl chloride and imidazole with an overall 38% yield [89JA6691]. An improved four-step preparation from bromomagnesio(trimethylsilyl)acetylide *via* [3-(trimethylsilyl)-2-propynilidene]--4-methylbenzenesulfonyl hydrazide gave a 40% yield of (trimethylsilyl)allene [83T935]. Moreover, attempted annulations of allenylsilanes employing ketones did not give satisfactory results [85JA7233], and no analogous transformations using aromatic aldehydes have been reported.

We now report a new and simple synthetic route to substituted furans and dihydrofurans using readily available 1-propargylbenzotriazole **3.1** as a three-carbon annulation unit. In chapter II, we described the preparation of 1-propargylbenzotriazole and some regioselective reactions of its mono- and dianions with electrophiles, which reactions can be directed to occur on either the sp- or the sp^3-hybridized carbon atom or at both these centers [92LA843]. The reactions of 1-(3-lithiopropargyl)benzotriazole (generated *in situ* from **3.1** and BuLi in THF) with aromatic aldehydes or ketones yielded the addition products **3.2** in high yields [92LA843]. These transformations have now been further developed to provide new routes to furans and to 2,5-dihydrofurans (Schemes 3.1 and 3.2).

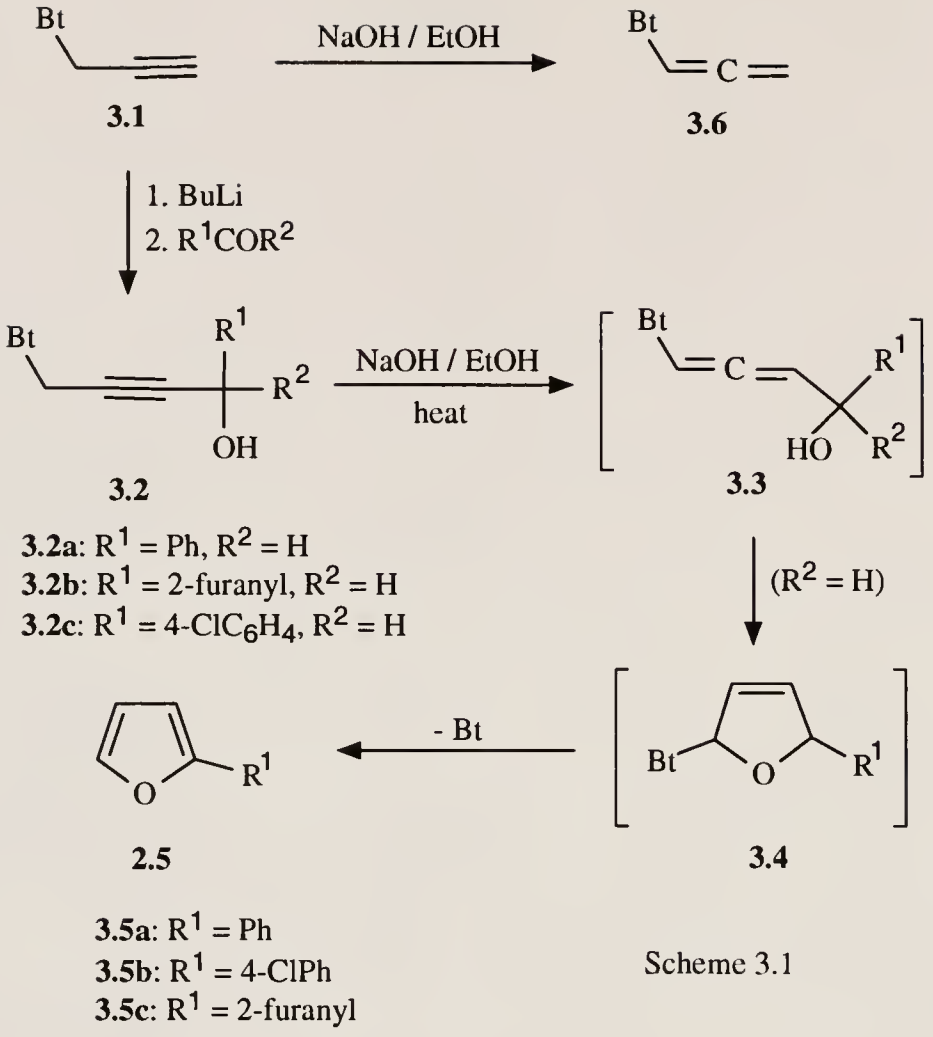
3.2 Results and Discussion

Compounds **3.2** derived from 1-propargylbenzotriazole **3.1** and aromatic aldehydes upon heating with ethanolic NaOH cyclized with the elimination of benzotriazole to give the corresponding 2-substituted furans **3.5** in 53-81% yield (Scheme 3.1, Table 3.1). This reaction is closely related to the previously reported

preparations of furans from 4-[(tetrahydropyran-2-yl)oxy]-2-butynolates [79AC875] or allenylaluminium reagents [82CL1029] with aldehydes. Evidently, the mechanism of the presently described process (Scheme 3.1) also includes an intermediate formation of α-allenyl alkoxides **3.3** (derived from the isomerization of the acetylenes **3.2**) followed by their intramolecular cyclization into 2,5-dihydrofurans **3.4**. The latter are readily aromatized under the reaction conditions with elimination of the benzotriazolyl anion to yield furans **3.5**). Significantly, the cycloeliminations of compounds **3.2** to furans **3.5** do not require treatment of the intermediate 2,5-dihydrofurans **3.4** with acids, which is essential for prior procedures [79AC875, 82CL1029]. Interestingly, in contrast to our reaction, **3.1** to **3.5**, (Scheme 3.1), [3+2] annulation of the lithio derivative of methoxyallene with ketones and aldehydes occurred *via* an attack of C-1 of the reagent on the carbonyl group of substrates and yielded 3-methoxy-2,5-dihydrofurans or, depending on steric factors, vinyl epoxides [84JCS(C)804]. The feasibility of the acetylene - allene isomerization of **3.2** into **3.3** is demonstrated by the easy transformation of 1-propargylbenzotriazole **3.1** into 1-allenylbenzotriazole **3.6** under the reaction conditions (Scheme 3.1).

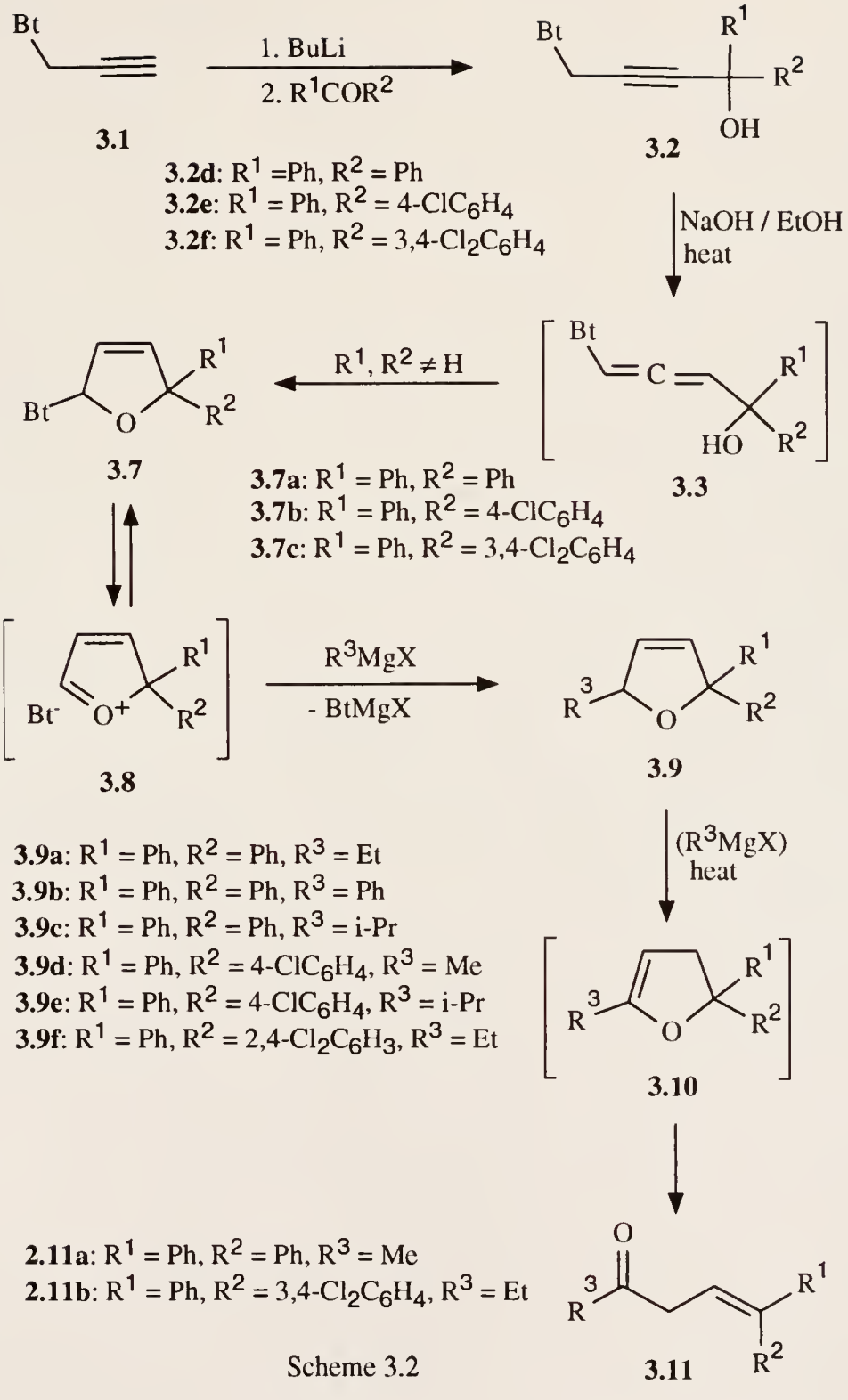
An analogous [3+2] annulation of **3.1** with aromatic ketones resulted in the formation of 1-(5,5-diaryl-2,5-dihydrofuran-2-yl)benzotriazoles **3.7** in 68-90% yield (Scheme 3.2). 2,5-Dihydrofurans **3.7b,c** have been isolated as mixtures of two diastereomers in ratios of ca. 1:1.3 and 1:1.5, respectively (by ^{1}H and ^{13}C NMR spectra). By contrast to the analogous intermediates **3.4** derived from **3.1** and aldehydes, compounds **3.7** were found to be relatively stable under basic conditions.

Previous papers from this laboratory demonstrated that benzotriazole-derived aminals reversibly ionize to yield the benzotriazolyl anion and iminium cations, as shown by the structure reactivity dependence observed, cross-over experiments, and



Scheme 3.1

the conductivity of these compounds in solutions (for a review see 91T2683). Due to such ionization, aminals of this type were able to undergo the replacement of the benzotriazole auxiliary group by Grignard and other organometallic reagents resulting in the introduction of various carbon substituents [91T2683, 91JCS(P1)2199]. In view of the similar reactivity of benzotriazole-derived N,O- and N,S-acetals, an analogous S_N1 mechanism is also assumed for similar transformations in the sulfur [91HCA1924] and oxygen series [91S69]. The reactivity of these compounds towards



3.1

3.2

3.2d: R^1 =Ph, R^2 = Ph
3.2e: R^1 = Ph, R^2 = 4-ClC_6H_4
3.2f: R^1 = Ph, R^2 = 3,4-$Cl_2C_6H_4$

3.3

3.7

3.7a: R^1 = Ph, R^2 = Ph
3.7b: R^1 = Ph, R^2 = 4-ClC_6H_4
3.7c: R^1 = Ph, R^2 = 3,4-$Cl_2C_6H_4$

3.8

3.9

3.9a: R^1 = Ph, R^2 = Ph, R^3 = Et
3.9b: R^1 = Ph, R^2 = Ph, R^3 = Ph
3.9c: R^1 = Ph, R^2 = Ph, R^3 = i-Pr
3.9d: R^1 = Ph, R^2 = 4-ClC_6H_4, R^3 = Me
3.9e: R^1 = Ph, R^2 = 4-ClC_6H_4, R^3 = i-Pr
3.9f: R^1 = Ph, R^2 = 2,4-$Cl_2C_6H_3$, R^3 = Et

3.10

2.11a: R^1 = Ph, R^2 = Ph, R^3 = Me
2.11b: R^1 = Ph, R^2 = 3,4-$Cl_2C_6H_4$, R^3 = Et

3.11

Scheme 3.2

Grignard reagent increases in a parallel with the degree of a substitution at the acetal carbon atom, in agreement with S_N1 but not with the alternative S_N2 mechanism (cf. 91HCA1924: the displacement of benzotriazolate anion in [(α-alkylthio)*tert*-alkyl]-benzotriazoles occurs smoothly, but fails for *sec*-alkyl N,S-acetals of this type 91HCA1924.).

We have now found that 2,5-dihydrofurans of type **3.7** bearing a benzotriazol-1-yl substituent in the 2-position of the heterocyclic ring can also serve as substrates in transformations of this type. Thus, compounds **3.7** upon heating with Grignard reagents in toluene yielded 2,5,5-trisubstituted 2,5-dihydrofurans **3.9** in 82-95% yields (Scheme 3.2). Analogously to the previously reported transformations of benzotriazole-derived aminals, and of N,O- and N,S-acetals [91T2683, 91HCA1924, 91S69], our new reaction **3.7** to **3.9** probably also occurs by a S_N1-mechanism involving ionization of the N-C bond of the N,O-acetal fragment of the 2,5-dihydrofurans **3.7** to generate cationic species **3.8**, which then couples with the Grignard reagent to yield the product **3.9** (Scheme 3.2).

Interestingly, prolonged heating of compounds **3.7** with an excess of Grignard reagent in toluene resulted in the formation of β,γ-unsaturated ketones **3.11** (Scheme 3.2). The formation of compounds **3.11** probably involved a base-assisted isomerisation of initially formed 2,5-dihydrofurans **3.9** to 2,3-dihydrofuran derivatives **3.10**, followed by the ring cleavage in dihydrofurans **3.10** to give ketones **3.11**. The latter process probably occurred *via* a deprotonation of the allylic position in compounds **3.10**. Previously, conversion of 2,5-dihydrofurans into their thermodynamically more stable 2,3-dihydro isomers was achieved by heating then with t-BuOK in t-BuOH [50BSF668]. Base-induced cleavage of the tetrahydrofuran ring has also been reported [72JOC560].

In conclusion, 1-propargylbenzotriazole **3.1** has been shown to be a useful reagent for new and potentially quite general synthetic routes to furan and 2,5-dihydrofuran derivatives. The presence of the benzotriazol-1-yl substituent in the compounds of type **3.7** enables additional functionalizations of these 2,5-dihydrofurans (cf. with 91T2683).

3.3 Experimental

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$. NMR spectra were taken in $CDCl_3$ except for compounds **3.7** which were recorded in $(CD_3)_2SO$, with tetramethylsilane as internal standart for ^1H (300 MHz) or solvent for ^{13}C (75MHz). Tetrahydrofuran was distilled under nitrogen immediately before use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out in atmospheres of argon or nitrogen. Column chromatography was conducted with silica gel grade 60-200 mesh. Compounds **3.1**, **3.2a-f** were prepared analogously to literature procedures [92LA843]. Analytical data for new compounds **3.2c**,**e**,**f** are given below.

1-Hydroxy-4-(benzotriazol-1-yl)-1-(4-chlorophenyl)but-2-yne (**3.2c**): Needles, yield 75%: mp 164-5 °C (from ethanol). IR 3370 cm^{-1} (OH); ^1H NMR δ 5.41 (s, 1 H, CH), 5.59 (s, 2 H, CH_2), 7.29 (d, J = 8.5 Hz, 2 H, Ar), 7.39-7.44 (m, 3 H, Bt and Ar, overlapped), 7.52 (dd, J = 8.3 and 6.9 Hz, 1 H, Bt), 7.75 (d, J = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 37.2 (CH_2), 61.5 (CHOH), 76.4 ($CH_2C{\equiv}C$), 86.2 ($C{\equiv}C$), 109.2 (Bt), 118.6 (Bt), 123.2 (Bt), 126.6 (Bt), 127.0 (2 C, Ar), 127.3 (2 C, Ar), 131.4 (Ar), 132.2 (Bt), 138.9 (Ar), 144.9 (Bt). Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11.

Found: C, 64.63; H, 4.14; N, 14.21.

1-Hydroxy-4-(benzotriazol-1-yl)-1-(4-chlorophenyl)-1-phenylbut-2-yne (**3.2e**): Needles, yield 80%: mp 130-1 °C (from ethanol). IR 3331 cm^{-1} (OH); ^1H NMR δ 5.52 (s, 2 H, CH_2), 7.21-7.50 (m, 11 H, Bt and Ar overlapped), 7.56 (d, *J* = 8.4 Hz, 1 H, Bt), 7.93 (d, *J* = 8.4 Hz 1 H, Bt); ^{13}C NMR δ 38.4 (CH_2), 73.7 (COH), 78.8 ($CH_2C{\equiv}C$), 89.2 ($C{\equiv}C$), 109.7 (Bt), 119.7 (Bt), 124.2 (Bt), 125.9 (C, Ar), 127.4 (2 C, Ar), 127.5 (Bt), 128.0 (2 C, Ar), 128.3 (4 C, Ar), 132.2 (Bt), 133.6 (Ar), 143.0 (Ar), 143.9 (Ar), 145.7 (Bt). Anal. Calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.63; H, 4.26; N, 11.17.

1-Hydroxy-4-(benzotriazol-1-yl)-1-(3,4-dichlorophenyl)-1-phenylbut-2-yne (**3.2f**): Needles, yield 78%: mp 137-8 °C (from ethanol). IR 3373 cm^{-1} (OH); ^1H NMR δ 5.95 (s, 2 H, CH_2), 7.16 (s, 1 H, OH), 7.25-7.64 (m, 9 H, Bt and Ar), 8.00 (d, *J* = 8.5 Hz, 1 H, Bt), 8.10 (d, *J* = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 37.7 (CH_2), 72.0 (COH), 80.1 ($CH_2C{\equiv}C$), 87.9 ($C{\equiv}C$), 110.7 (Bt), 119.3 (Bt), 124.3 (Bt), 125.5 (2 C, Ar), 126.0 (Ar), 127.3 (Bt), 127.6 (2 C, Ar), 128.2 (2 C, Ar), 130.0 (Ar), 130.4 (Ar), 130.8 (Ar), 132.4 (Bt), 144.7 (Ar), 145.3 (Bt), 146.9 (Ar); Anal. Calcd. for $C_{22}H_{15}Cl_2N_3O$: C, 64.72; H, 3.70; N, 10.29. Found: C, 64.94; H, 3.68; N, 10.27.

3.3.1 General Procedure for the Preparation of 2-Substituted Furans (**3.5a-b**)

A mixture of the appropriate alcohol **3.2a-c** (5 mmol) and sodium hydroxide (0.4 g, 10 mmol) in ethanol (50 ml) was refluxed for 12 hr. Water (30 ml) and ethyl ether (50 ml) were added. The organic phase was separated, washed with water (3 x 30 ml) and dried ($MgSO_4$). Solvent was distilled *in vacuo* and the crude product purified by column chromatography or by recrystallization.

2-Phenylfuran (**3.5a**): Purified by column chromatography (chloroform). ^{1}H NMR ($CDCl_3$) δ 6.41 (dd, *J* = 2.1 and 1.5 Hz, 1 H, H-4 of furan), 6.60 (d, *J* = 3.6 Hz, 1 H, H-3 of furan), 7.23 (d, *J* = 7.8 Hz, 1 H, Ph), 7.34 (dd, *J* = 8.1 and 7.5 Hz, 2 H, Ph), 7.42 (d, *J* = 1.8 Hz, 1 H, H-5 of furan), 7.65 (d, *J* = 8.1 Hz, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ 104.9 (C-4 of furan), 111.6 (C-3 of furan), 123.7 (2 C, Ph), 127.3 (Ph), 128.6 (2 C, Ph), 130.8 (Ph), 142.0 (C-5 of furan), 153.9 (C-2 of furan).

2-(4-Chlorophenyl)furan (**3.5b**): Purified by recrystallization from ethanol. ^{1}H NMR ($CDCl_3$) δ 6.46 (dd, *J* = 3.3 and 1.8 Hz, 1 H, H-4 of furan), 6.63 (d, *J* = 3.4 Hz, 1 H, H-3 of furan), 7.34 (d, *J* = 9.0 Hz, 2 H, Ar), 7.45 (d, *J* = 1.8 Hz, 1 H, H-5 of furan), 7.58 (d, *J* = 8.8 Hz, 2 H, Ar); ^{13}C NMR δ 105.4 (C-4 of furan), 111.7 (C-3 of furan), 125.0 (2 C, Ar), 128.8 (2 C, Ar), 129.3 (Ar), 132.9 (Ar), 142.3 (C-5 of furan), 152.9 (C-2 of furan).

2,2′-Bifuryl (**3.5c**): Purified by column chromatography (chloroform - hexane 1:2). ^{1}H NMR ($CDCl_3$) δ 6.44 (dd, *J* = 3.4 and 1.8 Hz, 2 H, H-4 of furan), 6.54 (d, *J* = 3.4, 2 H, H-3 of furan), 7.40 (d, *J* = 1.8 Hz, 2 H, H-5 of furan); ^{13}C NMR δ 105.0 (C-4), 111.3 (C-3), 141.7 (5-C), 146.6 (C-2).

1-Allenylbenzotriazole (**3.6**): A mixture of 1-propargylbenzotriazole **3.1** (0.1 mol, 15.7 g) and sodium hydroxide (0.1mol, 4.0 g) in ethanol (50 ml) was stirred at 25 °C for 10 h. . Water (100 ml) was added and the mixture was extracted with diethyl ether (100 ml), washed with water (3 x 50 ml) and dried ($MgSO_4$). Solvent was evaporated *in vacuo* to give a crude oily product which was purified by recrystallization from cold diethyl ether. Needles, yield 9.42 g (60%): mp 45-46 °C; ^{1}H NMR ($CDCl_3$) δ 5.79 (d, *J* = 6.6 Hz, 2 H, CH_2), 7.34-7.47 (m, 2 H, Bt), 7.78 (m, 2 H, CH and Bt, overlapped), 8.04 (d, *J* = 8.4 Hz, 1 H, Bt); ^{13}C NMR δ 88.6 (CH_2), 97.7 (CH), 110.8 (Bt), 119.8 (Bt), 124.3 (Bt), 127.6 (Bt), 131.3 (Bt), 146.2 (Bt), 201.5 (C).

Anal. Calcd. for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.73. Found: C, 68.71; H, 4.47; N, 27.15.

3.3.2 General Procedure for the Preparation of 2-(Benzotriazol-1-yl)-5,5-diaryl-2,5-dihydrofurans (**3.7a-c**)

A mixture of the appropriate alcohol **3.2d-f** (10 mmol) and sodium hydroxide (0.40 g, 10 mmol) in ethanol (50 ml) was stirred at 60-80°C for 12 h. Water (50 ml) and ethyl ether (100 ml) were added. The organic phase was separated, washed with water (80 ml x 3) and dried ($MgSO_4$). Solvent was evaporated *in vacuo*, and the crude product recrystallized from ethanol.

2-(Benzotriazol-1-yl)-5,5-diphenyl-2,5-dihydrofuran (**3.7a**): ^{1}H NMR δ 6.30 (dd, *J* = 5.9 and 1.4 Hz, 1 H, H-2 of furan), 7.02 (dd, J = 5.9 and 2.1 Hz, 1 H, H-3 of furan), 7.17-7.42 (m, 13 H, Bt and Ph, overlapped), 7.55 (dd, *J* = 2.1 and 1.4 Hz, H-4 of furan), 8.02 (d, *J* = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 92.9 (C-2 of furan), 98.2 (C-5 of furan), 110.9 (Bt), 119.8 (Bt), 123.4 (C-3 of furan), 124.0 (Bt), 126.2 (4 C, Ph), 127.2 (Bt), 127.6 (Ph), 127.8 (Ph), 128.2 (2 C, Ph), 128.4 (2 C, Ph), 132.0 (Bt), 139.1 (C-4 of furan), 142.5 (Ph), 143.6 (Ph), 146.7 (Bt).

2-(Benzotriazo-1-yl)-5-(4-chlorophenyl)-5-phenyl-2,5-dihydrofuran (**3.7b**): A mixture of two diastereomers in a ratio of 1:1.3. ^{1}H NMR δ 6.35 (m, 1 H, H-2 of furan), 6.98 (m, 1 H, H-3 of furan), 7.16-7.38 (m, 1 H, Bt and Ar, overlapped), 7.53 (d, *J* = 7.3 Hz, 1 H, H-4 of furan), 8.05 (m, 1 H, Bt); ^{13}C NMR δ 92.3 (0.6 C, C-2 of furan), 92.5 (0.4 C, C-2 of furan), 95.4 (C-5 of furan), 110.3 (0.6 C, Bt), 110.5 (0.4 C, Bt), 119.3 (0.6 C, Bt), 119.4 (0.4 C, Bt), 123.4 (C-3 of furan), 123.8 (Bt), 127.0 (Bt), 125.7, 125.9, 127.1, 127.2, 127.3, 127.4, 127.6, 128.0, 128.1, 128.2 (9 C, Ar), 131.6 (0.6 C, Ph), 131.7 (0.4 C, Ph), 133.0 (0.6 C, Bt), 133.2 (0.4 C, Bt), 138.3 (C-4 of

furan), 141.0 (0.6 C, Ar), 141.8 (0.4 C, Ar), 142.0 (0.4 C, Ar), 142.8 (0.6 C, Ar), 146.1(0.6 C, Bt), 146.2 (0.4 C, Bt).

2-(Benzotriazol-1-yl)-5-(3,4-dichlorophenyl)-5-phenyl-2,5-dihydrofuran (**3.7c**): A mixture of two diastereomers in a ratio of 1:1.5. ^{1}H NMR δ 6.25 (m, 1 H, H-2 of furan), 6.85 (m. 1 H, H-3 of furan), 6.92-7.42 (m, 1 H, H-4 of furan), 6.92-7.42 (m, 12 H, Ar), 7.92 (m, 1H, Bt); ^{13}C NMR ($CDCl_3$) δ 92.4 (0.6 C, C-2 of furan), 92.7 (0.4 C, C-2 of furan), 95.1 (0.6 C, C-5 of furan), 95.2 (0.4 C, C-5 of furan), 110.3 (0.6 C, Bt), 110.6 (0.4 C, Bt), 119.8 (0.4 C, Bt), 119.9 (0.6 C, Bt), 124.1 (0.4 C, Bt), 124.2 (0.6 C, Bt), 125.9 (C-3 of furan), 127.4 (0.4 C, Bt), 127.6 (0.6 C, Bt), 125.5, 125.7, 125.8, 126.1, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6 (6 C, Ar), 130.2 (0.6 C, Ar), 132.3 (0.6 C, Ar), 132.5 (0.4 C, Ar), 138.1 (C-4 of furan), 141.5 (0.4 C, Ar), 142.4 (0.6 C, Ar), 142.9 (0.6 C, Ar), 143.9 (0.4 C, Ar), 146.5 (Bt).

3.3.3 General Procedure for the Preparation of 2,2,5-Trisubstituted-2,5-dihydrofurans (**3.9**)

1.0 M Grignard reagent in diethyl ether (4 mmol) was added dropwise at 25 °C with stirring to a solution of the appropriate compound **7a-c** (2 mmol) in toluene (20 ml). The mixture was refluxed for 2 h and cooled to 25 °C. Water (50 ml) was added, followed by extraction with diethyl ether (40 ml). The organic phase was washed with water (3 x 30 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue subjected to column chromatography (chloroform) to afford pure product.

2,2-Diphenyl-5-ethyl-2,5-dihydrofuran (**3.9a**): ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 3 H, CH_3), 1.55 (dq, J = 13.5 and 7.4 Hz, 2 H, CH_3), 4.82 (m, 1 H, H-5 of furan), 5.81 (dd, J = 5.9 and 1.3 Hz, 1 H, H-3 of furan), 6.16 (dd, J = 5.9 and 2.2 Hz, 1 H, H-4 of furan), 7.08-7.26 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 9.73 (CH_3), 28.7

(CH_2), 87.2 (C-5 of furan), 94.0 (C-2 of furan), 126.2, 126.5, 126.9, 128.0 (10 C, Ph), 129.5 (C-3 of furan), 132.8 (C-4 of furan), 145.6 (Ph), 145.8 (Ph).

2,2,5-Triphenyl-2,5-dihydrofuran (**3.9b**): ^{1}H NMR ($CDCl_3$) δ 5.94 (dd, J = 2.4 and 1.5 Hz, 1 H, H-5 of furan), 6.00 (dd, J = 5.9 and 1.5 Hz, 1 H, H-4 of furan), 6.44 (dd. J = 5.9 and 2.4 Hz, 1 H, H-3 of furan), 7.17-7.44 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 87.9 (C-5 of furan), 95.0 (C-2 of furan), 126.2, 126.8, 127.1, 127.2, 127.9, 128.1, 128.2 128.4, 128.7 (15 C, Ph), 130.2 (C-4 of furan), 132.8 (C-3 of furan), 140.8 (Ph), 145.2 (Ph), 145.3 (Ph).

2,2-Diphenyl-5-isopropyl-2,5-dihydrofuran (**3.9c**): ^{1}H NMR ($CDCl_3$) δ 0.77 (d, J = 6.8 Hz, 3 H, CH_3), 0.87 (d, J = 6.8 Hz, 3 H, CH_3), 1.73 (dq, J = 6.8 and 13.4 Hz, 1 H, CH), 4.56 (m, 1 H, H-5 of furan), 5.86 (dd, J = 6.0 and 1.4 Hz, 1 H, H-4 of furan, 6.23 (dd, J = 6.0 and 2.1 Hz, 1 H, H-3 of furan), 7.07-7.29 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_3), 18.9 (CH_3), 33.2 (CH), 91.4 (C-5 of furan), 93.9 (C-2 of furan), 126.2 (2 C, Ph), 126.9 (2 C, Ph), 127.9 (C-4 of furan), 128.0 (2 C, Ph), 128.3 (2 C, Ph), 133.3 (C-3 of furan), 145.7 (Ph), 145.8 (Ph).

2-(4-Chlorophenyl)-2-phenyl-5-methyl-2,5-dihydrofuran (**3.9d**): A mixture of two diastereomers in a ratio of 1:1. ^{1}H NMR ($CDCl_3$) δ 1.33 (dd, J = 6.4 and 6.5 Hz, 3 H, CH_3), 5.05 (m, 1 H, H-5 of furan), 6.18 (dd, J = 5.9 and 2.3 Hz, 1 H, H-3 of furan), 7.15-7.33 (m, 9H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.7 (CH_3), 81.9 (0.5 C, C-5 of furan), 82.0 (0.5 C, C-5 0f furan), 93.8 (0.5 C, C-2 of furan), 93.9 (0.5 C, C-2 of furan), 126.2, 126.4 (2 C, Ar), 127.1 (0.5 C, Ph), 127.2 (0.5 C, Ph), 127.8, 127.9, 128.0, 128.1 (6 C, Ar), 131 .4 (C-4 of furan), 131.9 (C-3 of furan), 132.8 (Ph), 144.0 (0.5 C, Ar), 144.6 (0.5 C, Ar), 144.8 (0.5 C, Ar), 145.4 (0.5 C, Ar).

2-Phenyl-2-(4-chlorophenyl)-5-isopropanyl-2,5-dihydrofuran (**3.9e**): A mixture of diastereomers in a ratio of 1:1.^{1}H NMR ($CDCl_3$) δ 0.75 (d, J = 6.7 Hz, 3 H,

CH_3), 0.84 (dd, J = 6.8 and 6.8 Hz, 3 H, CH_3), 1.68 (m, 1 H, CH), 4.63 (m, 1 H, H-5 of furan), 5.84 (m, 1 H, H-4 of furan), 6.16 (m, 1 H, 3-H of furan), 7.04-7.24 (m, 9 H, Ar); ^{13}C NMR ($CDCl_3$) δ 18.2 (0.5 C, CH_3), 18.3 (0.5 C, CH_3), 18.8 (CH_3), 33.1 (CH), 91.5 (C-5 of furan), 93.4 (0.5 C, C-2 of furan), 93.5 (0.5 C, C-2 of furan), 126.0 (Ar), 126.2 (Ar), 126.5 (2 C, Ar), 127.6 (Ar), 127.8 (Ar), 128.0 (Ar), 128.1 (2 C, Ar), 128.7 (C-4 0f furan), 132.7 (Ph), 132.8 (C-3 of furan), 144.3 (0.5 C, Ar), 144.5 (0.5 C, Ar), 145.2 (0.5 C, Ar), 145.3 (0.5 C, Ar).

2-(3,4-Dichlorophenyl)-2-phenyl-5-ethyl-2,5-dihydrofuran (**3.9f**): A mixture of diastereomers in a ratio of 1:1. ^{1}H NMR ($CDCl_3$) δ 0.82 (m, 3 H, CH_3), 1.53 (m, 2 H, CH_2), 4.81 (m, 1 H, H-5 of furan), 5.86 (dd, J = 6.0 and 1.2 Hz, H-4 of furan), 6.12 (dd, J = 6.0 and 2.2 Hz, 1 H, H-3 of furan), 7.00-7.30 (m, 7 H, Ar), 7.38 (s, 1 H, Ar); ^{13} C NMR ($CDCl_3$) δ 9.7 (0.5 C, CH_3), 9.8 (0.5 C, CH_3), 28.7 (CH_2), 87.5 (C-5 of furan), 93.2 (C-2 of furan), 125.7, 125.9, 126.0, 126.1, 126.2, 126.3, 127.2, 127.3, 128.1, 128.2, 128.3, 128.4, 128.6, 129.9 (8 C, Ar), 130.4 (C-4 of furan), 130.8 (Ph), 131.7 (C-3 of furan), 132.0 (0.5 C, Ar), 132.1 (0.5 C, Ar), 144.4 (0.5 C, Ar), 144.6 (0.5 C, Ar), 146.0 (0.5 C, Ar), 146.3 (0.5 C, Ar).

3.3.4 General Procedure for the Preparation of β,γ-Unsaturated Ketones (**3.11a,b**)

1.0 M Grignard reagent in diethyl ether (4 mmol) was added dropwise at 25 °C with stirring to a solution of the appropriate compound **7a,c** (2 mmol) in toluene (20 ml). The mixture was refluxed for 48 h and cooled to 25 °C. Water (50 ml) was added, followed by extraction with diethyl ether (40 ml). The organic phase was washed with water (3 x 30 ml) and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue subjected to column chromatography (chloroform - hexanes

1:1) to afford pure product as the major fraction.

5,5-Diphenylpent-4-ene-2-one (**3.11a**): IR 1712 cm^{-1} (OH); ^1H NMR δ 2.09 (s, 3 H, CH_3), 3.25 (d, J = 7.3 Hz, 2 H, CH_2), 6.28 (t, J = 7.3 Hz, 1 H, CH=), 7.11-7.40 (m, 10 H, Ph). ^{13}C NMR δ 29.7 (CH_3), 44.5 (CH_2), 120.4 (CH=), 127.2 (2 C, Ph), 128.0 (2 C, Ph), 128.2 (2 C, Ph), 128.3 (2 C, Ph), 129.5 (2 C, Ph), 139.3 (Ph), 141.7 (Ph), 144.6 (>C=), 206.4 (CO).

6-(3,4-Dichlorophenyl)-6-phenylhex-5-ene-3-one (**3.11b**): A mixture of two geometric isomers in a ratio of ca. 1.5:1. IR 1708 cm^{-1} (CO); ^1H NMR δ 0.95 (dd, J = 7.3 and 7.2 Hz, 3H, CH_3), 2.31 (m, 2H, CH_2CO), 3.14 (m, 2 H, CH_2), 6.23 (m, 1 H, CH=), 6.92-7.39(m, 8H, Ar); ^{13}C NMR δ 17.8 (CH_3), 36.1 (CH_2), 43.2 (CH_2CO), 122.0 (0.4 C, CH=, minor isomer), 122.5 (0.6 C, CH=, major isomer), 126.5, 127.2, 127.6, 127.7, 128.2, 128.5, 129.0, 129.1, 129.4, 129.5, 129.9, 130.3, 131.1, 131.4, 131.5, 132.2, 132.5, 138.2, 139.4, 140.8, 141.9 (12 C, Ar), 142.3 (0.4 C, >C=, minor isomer), 142.4 (0.6 C, >C=, major isomer), 208.6 (CO).

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* Assignments for ^{13}C NMR spectra in neccessary cases were confirmed by APT experiments.

Table **3.1** Preparation of Compounds **3.5a-c, 3.7a-c, 3.9a-f, 3.11a-b**

compd. no.	isolated yield (%)	mp (^{O}C) or bp (^{O}C)	crystal form	found (cacled) (%)			molecular formula	HRMS
				C	H	N		found (cacld) (%)
3.5a	81	94-96/10 Torr[a]	oil				$C_{10}H_8O$	144.0567(144.0575)
3.5b	62	75-76[b]	needles[c]				$C_{10}H_7O$	
3.5c	53	d	oil				$C_{10}H_7O$	134.0378(134.0368)
3.7a	77	169-170	needles[c]	78.04(77.86)	5.05(5.05)	12.43(12.43)	$C_{22}H_{17}N_3O$	
3.7b	68	151-152	needles[c]	70.67(70.68)	4.24(4.31)	11.24(11.24)	$C_{22}H_{16}ClN_3O$	
3.7c	90	56-57	needles[c]	64.67(64.72)	3.65(3.70)	10.22(10.29)	$C_{22}H_{15}Cl_2N_3O$	
3.9a	95		oil				$C_{18}H_{18}O$	250.1356(250.1358)
3.9b	86		oil				$C_{22}H_{18}O$	298.1361(298.1358)
3.9c	84		oil				$C_{19}H_{20}O$	264.1514(264.1514)
3.9d	87		oil				$C_{17}H_{15}ClO$	270.0811(270.0811)
3.9e	82		oil				$C_{19}H_{19}ClO$	298.1148(298.1124)
3.9f	90		oil	67.34(67.72)	4.92(5.05)		$C_{18}H_{16}O$	
3.11a	89		oil				$C_{17}H_{16}O$	236.1200(236.1201
3.11b	42		oil	67.57(67.72)	4.87(5.05)		$C_{18}H_{16}Cl_2O$	

[a][46JCS895], bp 92-95 ^{O}C Torr. [b][46JCS895], mp 74-75 ^{O}C. [c]From ethanol. [d][77JOC1680], oil.

CHAPTER IV
NEW SYNTHESIS OF 2-ARYL- AND 2-HETARYL-PYRROLES FROM 1-PROPARGYLBENZOTRIAZOLE

4.1 Introduction

Pyrrole and its derivatives are of enormous importance in organic and bio-chemistry, and found many applications in medicine and technology, as covered in numerous monographs and reviews (see 90MI177 and refs. cited therein). Various aryl- and hetaryl-substituted pyrroles are of pharmaceutical interest [84MI313, 84ZOR60] and as potential monomers for conducting polymers and nonlinear optics materials [84MI313, 92H2003].

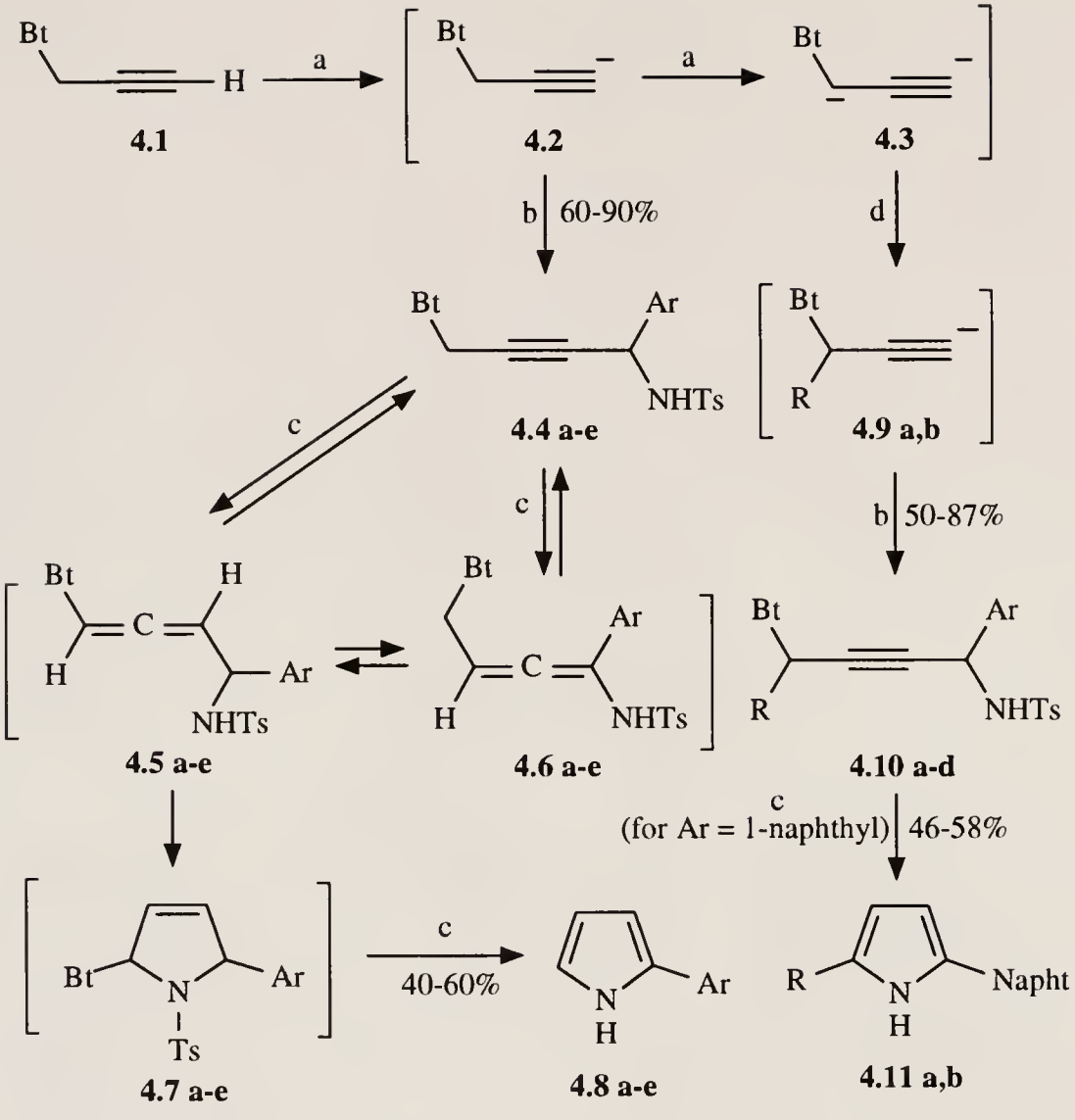
In chapter II, we described the preparation of 1-propargylbenzotriazole **4.1** and some regioselective reactions of its mono- and dianions with electrophiles which can be directed to occur either at the sp- or at the sp^3-hybridized carbon atom or at both these centres [92LA843]. The reactions of 1-(3-lithiopropargyl)benzotriazole **4.2** with carbonyl compounds enabled novel preparations of furans and of 2,5-dihydrofurans [93JOC3038, also see chapter II]. We have now extended these studies to provide a new and simple synthetic route to 2-aryl- and 2-hetaryl-pyrroles using readily available 1-propargylbenzotriazole **4.1** as a three-carbon annulation unit.

4.2 Results and Discussion

1-(3-Lithiopropargyl)benzotriazole **4.2** (generated *in situ* from **4.1** and BuLi in THF) reacted readily with N-tosylarylimines to give the corresponding adducts **4.4a-e**

in high yields (Scheme 4.1 and Table 4.1). The structures of **4.4a-e** were supported by analytical and spectral data, thus the ^{13}C NMR spectra displayed characteristic resonances for the acetylenic carbons in the region of 78-89 ppm. None of the isomeric allene derivatives **4.5** or **4.6** could be isolated from, or detected in, the reaction mixtures. Compounds **4.4** upon heating with ethanolic sodium hydroxide afforded 2-aryl- or 2-hetaryl-pyrroles **4.8a-e** in 40-60% yields. The mechanism of this novel transformation is probably closely related to that previously suggested for the base-assisted cycloeliminations of 1-hydroxy-4-benzotriazolyl-1-arylbut-2-ynes [93JOC3038], and involves an acetylene-allene isomerization of compounds **4.4a-e** to intermediates **4.5a-e** which further cyclize to 2,5-dihydropyrroles **4.7a-e**. This is then followed by heteroaromatization and N-deprotection with elimination of benzotriazole and of *p*-toluenesulfonic acid, respectively, to yield the pyrroles **4.8a-e** (Scheme 4.1 and Table 4.2).

As we demonstrated in chapter II [92LA843], 1-(1,3-dilithiopropargyl)-benzotriazole **4.3** can react with electrophilic reagents selectively in position 1 of the propargyl fragment to afford the corresponding mono-anions of the type **4.9** (Scheme 4.1). Analogous to the transformation of 1-(3-lithiopropargyl)benzotriazole **4.2** just described, intermediates **4.9a,b** (generated *in situ* from **4.2** and one equivalent of methyl or ethyl iodide) reacted with N-tosylarylimines to give compounds **4.10a-d** in high yields. Compounds **4.10a,b** were then cyclized by heating with ethanolic alkali to afford the corresponding 5-alkyl-2-(1-naphthyl)pyrroles **4.11a,b** in 46 and 58% yields, respectively.



4.4-4.8	Ar
a	Ph
b	2-thienyl
c	*p*-Tol
d	1-naphthyl
e	*p*-ClC_6H_4

4.9, 4.11	R
a	Me
b	Et

4.10	Ar	R
a	1-naphthyl	Me
b	1-naphthyl	Et
c	*p*-Tol	Me
d	*p*-ClC_6H_4	Et

Scheme 4.1
Reagents and conditions: a, BuLi/hexane/THF, -78 °C;
b, TsN = CHAr/THF, -78 ° to 25 °C, 4h;
c, NaOH/EtOH, 90 °C, 2 h; d, RI/THF, -78 °C, 30 min.

It should be noted however, that our attempted preparations of 5-alkyl-2-arylpyrroles from acetylenes **4.10c-d** were not successful and no pure compounds were isolated although traces of the expected products were detected by ^{1}H NMR. Although the exact reason remains unclear, in part, it can probably be accounted for by a concurrent isomerization of compounds **4.10c-d** into allenes of type **4.6** rather than to intermediates of type **4.5** required for the pyrrole ring formation. This probably results from a decreased acidity of the methyne(alkyl) group α to the benzotriazol-1-yl substituent, as compared to that of a methylene group in intermediates **4.4a-e** (Scheme 4.1). Indeed, our previous studies demonstrated an easy isomerization of 1-propargylbenzotriazole to 1-allenylbenzotriazole, whereas its α-alkyl substituted derivatives were relatively stable under basic conditions [92LA843, 93JOC3038].

Among the previously reported routes to 2-aryl- and 2-hetaryl-pyrroles, the Trofimov reaction of ketoximes with acetylenes (or their precursors) is the most important (for a review see 90MI177). However, application of this procedure to 2-naphthylpyrroles was accompanied by considerable resinification and gave low yields, e.g. 2-(1-naphthyl)pyrrole **4.8d** in 15% yield [82KGS1351]. Other reported preparations of 2-arylpyrroles include thermal rearrangement of 1-phenylpyrrole to 2-phenylpyrrole [41JA1563], a 4-step route *via* the Hemetsberger reaction of β-arylacroleins with methyl azidoacetate [79TL1717], the synthesis of 2,4-diphenylpyrrole by a rhodium-catalyzed hydroformylation of (1,3-diphenyl-propargyl)amine [91TL1093], and of 2-phenylpyrrole from 1-trimethylsilyl-*N*,*N*--bis(trimethylsilyl)propargylamine or from 1-phenyl-1-trimethylsiloxy-4-[*N*,*N*--bis(trimethylsilyl)amino]but-2-yne [92T6231]. The presently described synthesis of 2-aryl- and 2-hetaryl-pyrroles is complementary to previously reported [3+2]

constructions of the pyrrole ring also involving a formation of N-C(2) and C(4)-C(5) bonds *via* condensations of α-amino acids and their derivatives with β-dicarbonyl or α,β-unsaturated carbonyl compounds (see a review 84MI313 and refs. cited therein).

In conclusion, 1-propargylbenzotriazole **4.1** has been shown to be a useful reagent for new and convenient synthetic route to 2-aryl- and 2-hetaryl-pyrroles. The method is generally restricted to the preparation of 2-substituted pyrroles, but in certain cases enables also the synthesis of 5-alkyl-2-arylpyrroles.

4.3 Experimental

Melting points were determined with a hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer using TMS as an internal standard. HRMS were obtained on a Finnigan Mat 95 spectrometer. Elemental analyses were determined in this Department. Column chromatography was conducted over silica gel (230-400 mesh). N-Tosylarylimines were prepared by the literature procedure [81JCS(P1)2435].

4.3.1 1-Benzotriazol-1-yl-4-(N-tosyl)amido-4-arylbut-2-ynes **4.4**

A solution of *n*-butyllithium in hexane (4.4 mL, 11 mmol, 2.5 *M*) is added dropwise with stirring to a solution of 1-propargylbenzotriazole **4.1** (1.57 g, 10 mmol) in THF (50 mL) at -78° C. The mixture is stirred at this temperature for 45 min, and an appropriate N-tosylarylimine (10 mmol) in THF (20 mL) is added dropwise. The solution is stirred at -78° C for 4 hr. Water (100 mL) and diethyl ether (200 mL) are added. The organic phase is washed with water (3 x 50 mL) and dried ($MgSO_4$). The

solvent is removed under reduced pressure to give crude products which are purified by crystallization from EtOH.

4.3.2 1-Benzotriazol-1-yl-4-(N-tosyl)amido-4-aryl-1-alkylbut-2-ynes **4.10**

2.5 M Butyllithium in hexane (8.8 mL, 22 mmol) is added dropwise with stirring to a solution of 1-propargylbenzotriazole **4.1** (1.57 g, 10 mmol) in THF (80 mL) at -78° C. The mixture is stirred at this temperature for 1 hr and an alkyl iodide (11 mmol) is added slowly. The mixture is stirred for several hours, until the blue color of the reaction disappeared. N-Tosylarylimine (10 mmol) in THF (30 mL) is added slowly at -78° C and the mixture is stirred for 4 hr. Water (150 mL) and diethyl ether (200 mL) are added. The organic phase is washed with water (3 x 50 mL) and dried ($MgSO_4$). The solvent is removed under reduced pressure to give the crude products which are purified by recrystallization from EtOH.

4.3.3 2-Arylpyrroles 4.8 and 2-(1-Naphthyl)-5-alkylpyrroles **4.11**

A mixture of the appropriate compound **4.4** or **4.10** (5 mmol) and sodium hydroxide (0.8 g, 20 mmol) is refluxed in ethanol (50 mL) for 12 hr. Water (50 mL) and ethyl ether (100 mL) are added. The organic phase is washed with water (3 x 30 mL) and dried ($MgSO_4$). The solvent is removed under reduced pressure, and the products are separated by column chromatography using eluents indicated in Table 4.2.

Table **4.1** Products **4.4** and **4.10** from Lithiated 1-Propargylbenzotriazole **4.1**

Product	Yield[a] (%)	mp (^{o}C)[b]	Crystal Form[c]	Molcular Formula[d]
4.4a	81	155-156	Needles	$C_{23}H_{20}N_4O_2S$ (416.5)
4.4b	82	142-143	Plates	$C_{21}H_{19}N_4O_2S_2$ (423.5)
4.4c	72	168-170	Plates	$C_{24}H_{22}N_4O_2S$ (430.6)
4.4d	92	197-198	Prisms	$C_{27}H_{22}N_4O_2S$ (466.6)
4.4e	76	154-155	Needles	$C_{23}H_{19}N_4ClO_2S$ (450.9)
4.10a	77	192	Plates	$C_{28}H_{24}N_4O_2S$ (480.6)
4.10b	72	177	Plates	$C_{29}H_{26}N_4O_2S$ (494.6)
4.10c	81	121	Needles	$C_{25}H_{24}N_4O_2S$ (444.6)
4.10d	76	135	Plates	$C_{25}H_{23}N_4ClO_2S$ (479.0)

[a] Yields are of purified products based on 1-propargylbenzotriazole **4.1**.
[b] Melting points are uncorrected.
[c] All products were recrystallized from EtOH.
[d] Satisfactory microanalysis obtained: C $\pm$ 0.40, H $\pm$ 0.17, N $\pm$ 0.26.

Table **4.2** 2-Arylpyrroles **4.8** and 2-(1-Naphthyl)-5-alkylpyrroles **4.11**

Product	Yield[a] (%)	mp (^{o}C)[b]	Lit. mp (^{o}C) or Molecular Formula[a]	Eluent (hexane/CH_3Cl)
4.8a	51	129	129-130 [41JA1563]	1 : 1
4.8b	60	154	154 [79TL1717]	1 : 2
4.8c	45	153	153 [1904CB2796]	1 : 1
4.8d	58	176-178	174-180 [82KGS1351]	1 : 2
4.8e	47	139	140 [85KGS1501]	1 : 2
4.11a	56	oil	$C_{15}H_{13}N$ (207.3)	1 : 2
4.11b	43	oil	$C_{16}H_{15}N$ (221.3)	1 : 2

[a] Isolated Yields.
[b] Satisfactory mass spectral data obtained.

Table **4.3** ^{1}H NMR Data of Products **4.4** and **4.10** δ, J (Hz)

Product	Bt				CH_3	CH_2	CH	NH	Aromatic
	H (4)	H (5)	H (6)	H (7)					
4.4a[a]	8.09(d, J=8.3)	7.46(t, J=8.3)	7.58 (m)	7.76(d , J=8.3)	2.28(s)	5.55(s)	5.32(s)	8.69 (br.s)	7.10(d, 2 H, J=8.3), 7.27-7.40(m, 5 H), 7.60(d, 2 H, J=8.3)
4.4b[c]	8.03(d, J=8.3)	7.4(t,, J=8.3)	7.50(d, J=8.4)	7.59(d, J=8.4)	2.34(s)	5.28(s)	5.32(d, J = 8.6)	8.2(d,, J=8.6)	7.03(d, 1 H, J=3.2), 7.07(d, 2 H, J=8.6), 7.23(d, 1 H, J=3.1), 7.24(d, 1 H, J=3.1), 7.66(d, 2 H, J=8.6)
4.4c[d]	8.03(d, J=8.3)	7.42(t, J=8.3)	7.52(t, J=8.3)	7.69(d, J=8.3)	2.27(s) 2.29(s)	5.4(s)	5.23(s)	8.55 (br.s)	7.05(d, 2 H, J=8.5), 7.06(d, 2 H, J=8.5), 7.26(d, 2 H, J=8.1), 7.61d 2 H, J=8.1)
4.4d[d]	8.04(d, J=8.3)	7.42 (m)[b]	7.52 (m)[b]	7.85(d, J=8.3)	2.32(s)	5.39(s)	5.97(s)	8.62 (br.s)	7.08(d, 2 H, J=8.4), 7.37-7.53(m, 3H), 7.65(d, 2 H, J=8.4), 7.64-7.70(m, 2 H), 7.89(m, 1 H), 8.23(m, 1 H)
4.4e[d]	8.04 (d, J=8.1)	7.43 (m)[b]	7.55 (m)[b]	7.85(d, J=8.3)	2.30(s)	5.48(s)	5.30(s)	8.70 (br.s)	7.06(d, 2 H, J=8.0), 7.29(d, 2 H, J=8.4), 7.39(d, 2 H, J=8.4), 7.59(d, 2 H, J = 8.0)
4.10a[a, e]	8.08 (m)	7.33 (m)	7.55 (m)	7.70(d, J=8.1)	1.43(d, J=6.8), 2.08(s)	-	7.7(m) 5.84(bs)	8.55 (br.s)	6.96(d, 2 H, J=8.0), 7.21-7.35(m, 4 H), 7.52-7.58(m, 3 H), 7.69-7.76(m, 1 H), 7.88(d, 1 H, J=8.2)
4.10b[c, e]	8.00 (m)	7.29 (m)	7.51 (m)	7.76(d, J=8.3)	0.81(t, J=7.4), 2.30(s)	2.00(dt, J=7.4 and 7.3)	5.39(t, J=7.4) 5.63(d, J=8.5)	6.09(d, J=8.5)	6.95(d, 2 H, J=8.1), 7.24-7.34(m, 2 H), 7.46-7.62(m, 5 H), 7.82(m, 1 H), 8.22(m, 1 H)
4.10c[c, e]	8.04(d, J=8.4)	7.35(t, J=7.8)	7.4(t, J=8.3)	7.58(d, J=8.2)	1.72(d, J=7.1), 2.14(s) 2.32(s)	-	5.31-5.42(m) 5.67(m)	5.31-5.42(m)	7.05(d, 2 H, J=8.5), 7.07(d, 2 H, J=7.9), 7.25(d, 2 H, J=7.9), 7.64(d, 2 H, J=8.5)
4.10d[c, e]	7.89(d, J=7.8)	7.27-7.39(m)	7.27-7.39(m)	7.52 7.57(m)	0.79(m) 2.29(s)	1.99(m) 2.29(s)	5.33-5.47(m)	6.70(m)	7.07(d, 2 H, J=8.1), 7.16(d, 2 H, J=8.5), 7.32(d, 2 H, J=8.5), 7.65(d, 2 H, J = 8.1)

[a] In DMSO-d_6. [b] Overlapped with other aromatic signals. [c] In $CDCl_3$. [d] In a mixture of DMSO-d_6 and $CDCl_3$.
[e] Signals of diasteraomers.

Table **4.4** ^{13}C NMR Data of Products **4.4** and **4.4** δ

Product	Bt						CH_3		CH_2	CH	C≡C	Aromatic
	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}						
4.4a[a]	119.2	127.5	124.2	110.7	145.2	132.2	20.9	37.4	48.1	78.4, 83.2		126.5 (2 C), 127.0, 127.9, 128.4, 129.1 (2 C), 138.0, 138.1, 142.5
4.4b[b]	118.9	126.9	123.5	109.5	145.2	131.6	20.7	37.3	44.0	75.9, 83.1		125.7, 126.0, 126.3 (2 C), 128.4 (2 C), 137.2, 137.8, 142.2
4.4c[c]	118.9	127.1	123.8	110.3	145.2	132.0	20.7 21.0	37.5	47.9	77.8, 83.2		126.4 (2 C), 126.7 (2 C), 128.5 (2 C), 128.6 (2C), 134.6, 137.1, 137.8, 142.1
4.4d[c]	118.9	127.0	123.7	110.3	145.1	131.9	20.9	37.4	45.8	78.5, 82.7		123.0, 124.5, 125.4, 125.5, 126.1, 126.5 (2C), 128.2, 128.5(2C), 128.7, 129.4, 132.6, 133.1, 137.5, 142.1
4.4e[c]	119.0	127.1	123.8	110.3	145.1	132.0	21.0	31.4	47.5	78.3, 82.6		126.4 (2 C), 128.0 (2 C), 128.5 (2 C), 128.7 (2C), 132.7, 136.6, 137.6, 142.3
4.10a[a]	119.3	127.4	123.3	111.0	145.5	131.2	20.9 21.4	-	45.8 46.2	82.6, 82.8		124.2 (2 C), 125.0, 125.7, 126.0, 126.5, 126.7 (2C), 128.6, 129.1 (2 C), 129.7, 132.9, 133.4, 137.9, 142.6
4.10b[b]	119.8	126.9	123.0	110.5	146.2	131.6	10.5 21.5	29.2	46.9 53.2	82.9, 83.7		123.9, 124.8 (2 C), 125.7, 126.0, 127.1 (2 C), 128.6, 129.0(2C), 129.6, 129.9, 131.3, 133.8, 136.8, 143.4
4.10c[c]	120.0	127.3	124.0	110.4	146.4	131.3	21.0, , - 21.8 21.4		47.1 48.8	82.2, 83.2		127.0 (2 C), 127.2 (2 C), 129.3 (2 C), 129.4 (2C), 133.8, 137.2, 138.4, 143.6
4.10d[c]	119.6	127.1	123.9	110.3	143.3	131.2	10.3 21.3	29.0	48.3 53.0	81.5, 83.1		126.8 (2 C), 128.4 (2 C), 128.5 (2 C), 129.0 (2C), 133.9, 135.4, 136.7, 136.8

[a] In DMSO-d_6. [b] In $CDCl_3$. [c] In a mixture of DMSO-d_6 and $CDCl_3$.

Table **4.5** ^{1}H NMR Data of 2-Arylpyrroles **4.8** and 5-Alkyl-2-naphthylpyrroles **4.11** ($CDCl_3$), δ, *J* (Hz)

Product	Pyrrole			CH_3	CH_2	NH	Aromatic
	H (3)	H (4)	H (5)				
4.8a	6.43 (m, 1 H)	6.19 (m, 1 H)	6.66 (m, 1 H)	-	-	8.23 (b r.s, 1 H)	7.08 (m, 1 H), 7.22 (m, 2 H), 7.31 (m, 2 H)
4.8b	6.43 (m, 1 H)	6.26 (m, 1 H)	6.74 (d, 1 H, J=1.3)	-	-	8.23 (br.s, 1 H)	7.11 (m, 1 H), 7.21 (m, 1 H), 7.92 (m, 1 H)
4.8c	6.47 (m, 1 H)	6.28 (m, 1 H)	6.80 (m, 1 H)	2.34 (s, 3 H)	-	8.37 (br.s, 1 H)	7.15 (d, 2 H, J = 7.9), 7.35 (d, 2 H, J = 7.9)
4.8d	6.34 (m, 1 H)	6.22 (m, 1 H)	6.64 (m, 1 H)	-	-	7.93 (br.s, 1 H)	7.18-7.33 (m, 4 H), 7.58 (m, 1 H), 7.68 (m, 1 H), 8.10 (m, 1 H)
4.8e	6.43 (m, 1 H)	6.22 (m, 1 H)	6.78 (m, 1 H)	-	-	8.34 (br.s, 1 H)	7.24 (d, 2 H, J = 8.8), 7.31 (d, 2 H, J = 8.8)
4.11a	6.31 (m, 1 H)	5.98 (m, 1 H)	-	2.29 (s, 3 H)	-	8.00 (br.s, 1 H)	7.35-7.43 (m, 4 H), 7.68 (m, 1 H), 7.77 (m, 1 H), 8.28 (m,1 H)
4.11b	6.31 (m, 1 H)	5.99 (m, 1 H)	-	1.21 (s, 3 H)	2.60 (q, 2 H, J = 7.6)	7.95 (br.s, 1 H)	7.31-7.40 (m, 4 H), 7.65 (m, 1 H), 7.76 (m, 1 H), 8.26 (m, 1 H)

Table **4.6** ^{13}C NMR Data of 2-Arylpyrroles **4.8** and 5-Alkyl-2-naphthylpyrroles **4.11** ($CDCl_3$), δ

Product	Pyrrole				CH_3	CH_2	Aromatic
	C (2)	C (3)	C (4)	C (5)			
4.8a	131.9	109.9	105.8	118.9	-	-	123.7 (2 C), 126.1, 128.8 (2 C), 132.6
4.8b	130.7	109.9	105.3	118.4	21.1	-	123.8 (2 C), 127.0, 129.5 (2 C), 135.8
4.8c	128.4	109.6	105.9	125.2	-	-	116.3, 118.0, 126.2, 134.3
4.8d	130.2	109.3	109.2	118.3	-	-	125.2, 125.6, 125.8, 125.9, 126.1, 127.3, 128.2, 131.1, 131.3, 133.8
4.8e	130.9	110.2	106.3	119.1	-	-	124.9 (2 C), 128.9 (2 C), 131.1, 131.6
4.11a	129.1	109.8	107.3	128.6	13.1	-	125.4, 125.5, 125.8 (2 C), 126.1, 127.0, 128.3, 131.2, 131.7, 134.0
4.11b	131.1	109.5	105.5	128.8	13.6	21.0	125.3, 125.4, 125.7, 126.0 (2 C), 126.9, 128.2, 131.6, 133.9, 135.0

CHAPTER V
A NOVEL FURAN RING CONSTRUCTION AND SYNTHESES OF 4- AND 4,5-SUBSTITUTED 2-(α-HETEROCYCLO)ALKYLFURANS

5.1 Introduction

The synthesis of furans is of importance since the furan ring is present in numerous natural compounds which exhibit interesting biological activities [93JOC21]. The ring system is also found in industrially significant substances and in many useful synthetic building blocks [84MI657 and 86CR795]. A variety of approaches leading to the generation of the furan ring have been documented [84MI657, 66MI377, 93JOC3038 and 93SL905] and among them, several general methods utilize an intramolecular cycloaddition of alkoxides to double and triple bonds as the key reaction. Recently, many acyclic precursors have been employed for the synthesis of a wide range of substituted furans [94H223]. For example, alkynyloxiranes, prepared by coupling vinylic halides or triflates with terminal alkynes followed by epoxidation with *m*-CPBA, are isomerized under strongly basic conditions or reduced with samarium diiodide / Pd to afford 2,4-, 2,5- and 2,3,5-substituted furans [94H223, 91JOC1683, 92JACS1450 and 93JOC3435], in a reaction pathway involving 5-*endo-dig* cyclization of the corresponding cumulenyl alkoxides.

In chapter II, III, IV and VI, we demonstrated that 1-propargylbenzotriazole (**5.1**), readily available from the reaction of benzotriazole with propargyl bromide in the presence of sodium hydroxide [92LA843], is a useful reagent for the synthesis of

furans, dihydrofurans [93JOC3038], pyrroles [94S93] and indoles [95UP1]. Thus, the reactions of 1-(3-lithiopropargyl)benzotriazole (**5.4**) with aromatic aldehydes give 1-[(3-hydroxyarylmethyl)propargyl]benzotriazoles which undergo base-assisted rearrangement to form α-hydroxyallenes. Subsequent intramolecular cyclization to 2-(benzotriazol-1-yl)-5-aryldihydrofurans and elimination of benzotriazole affords 2-arylfurans [93JOC3038].

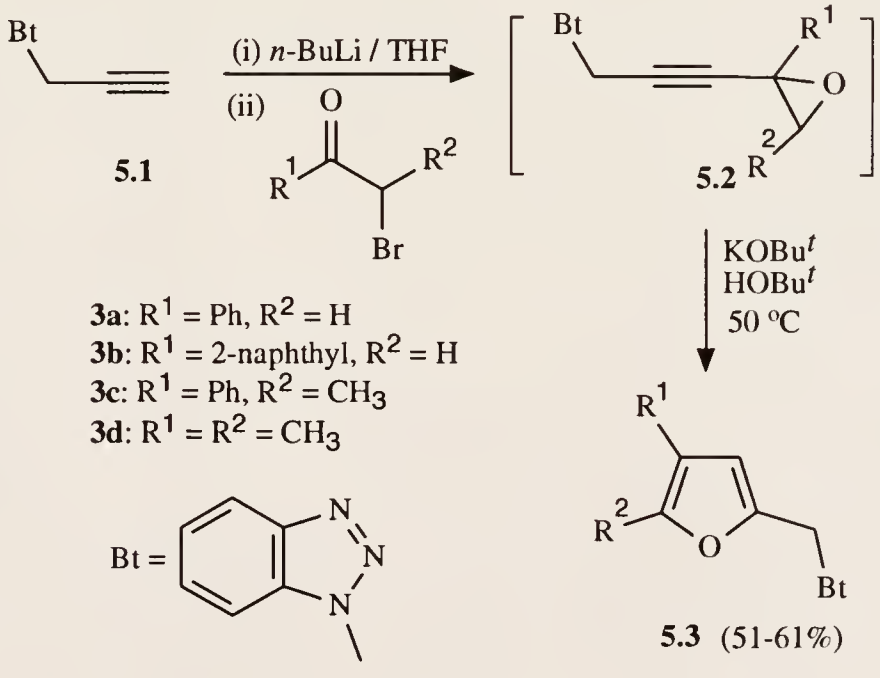
We now report a novel one-pot procedure for furan ring construction from 1-propargylbenzotriazole (**5.1**) and α-bromoketones. The resulting 4- and 4,5-substituted 2-(benzotriazol-1-yl)methylfurans can undergo, either directly or following alkylation, displacement of the benzotriazole groups by other heterocycles to give the corresponding 4- and 4,5-substituted 2-(α-heterocyclo)alkylfurans **5.10** and **5.12**. Compounds of types **5.10** and **5.12** play important roles in the food industry and as intermediates for the synthesis of other organic compounds and polymers [93JOC4376]. Few previous methods are reported for the synthesis of **5.10** and **5.12**. In particular, such systems with two different simple heterocyclic rings were unknown until our previous work [93JOC4376].

5.2 Results and Discussion

5.2.1 Furan ring construction - Preparation of 4- and 4,5-substituted 2-(benzotriazol-1-yl)methylfurans **5.3**

As an extension of our investigation concerning the reactivity of lithiated 1-propargylbenzotriazole (**5.4**) towards ketones for the preparation of dihydrofurans [93JOC3038, also see chapter III], we found that treatment of 1-propargylbenzotriazole (**5.1**) with one equivalent of *n*-BuLi followed by quenching with one

equivalent of α-bromoketone at -78 °C and subsequent warming to room temperature gave the corresponding alkynyloxirane **5.2** as the major product with smaller amounts of the substituted furan **5.3**. The structures of both derivative **5.2** and **5.3** were supported by ^{1}H and APT NMR spectra. When the reaction was carried out at -78 °C without warming, the alkynyloxirane **5.2** could be isolated exclusively (as was done for **5.2d**, R^1=R^2=CH_3, see experimental). Assuming that product **5.3** was formed *via* isomerization of intermediate **5.2** in the presence of a trace of base, we treated alkynyloxirane **5.2** with KOBu^t in HOBu^t at 50 °C for several hours. The expected product **5.3** was afforded in good yield. Similar base-catalyzed transformations of alkynyloxiranes into furans are found in the literature, however, the corresponding alkynyloxiranes are prepared by multi-step methods and 18-crown-6 is required for the ring formation [92JACS1450].

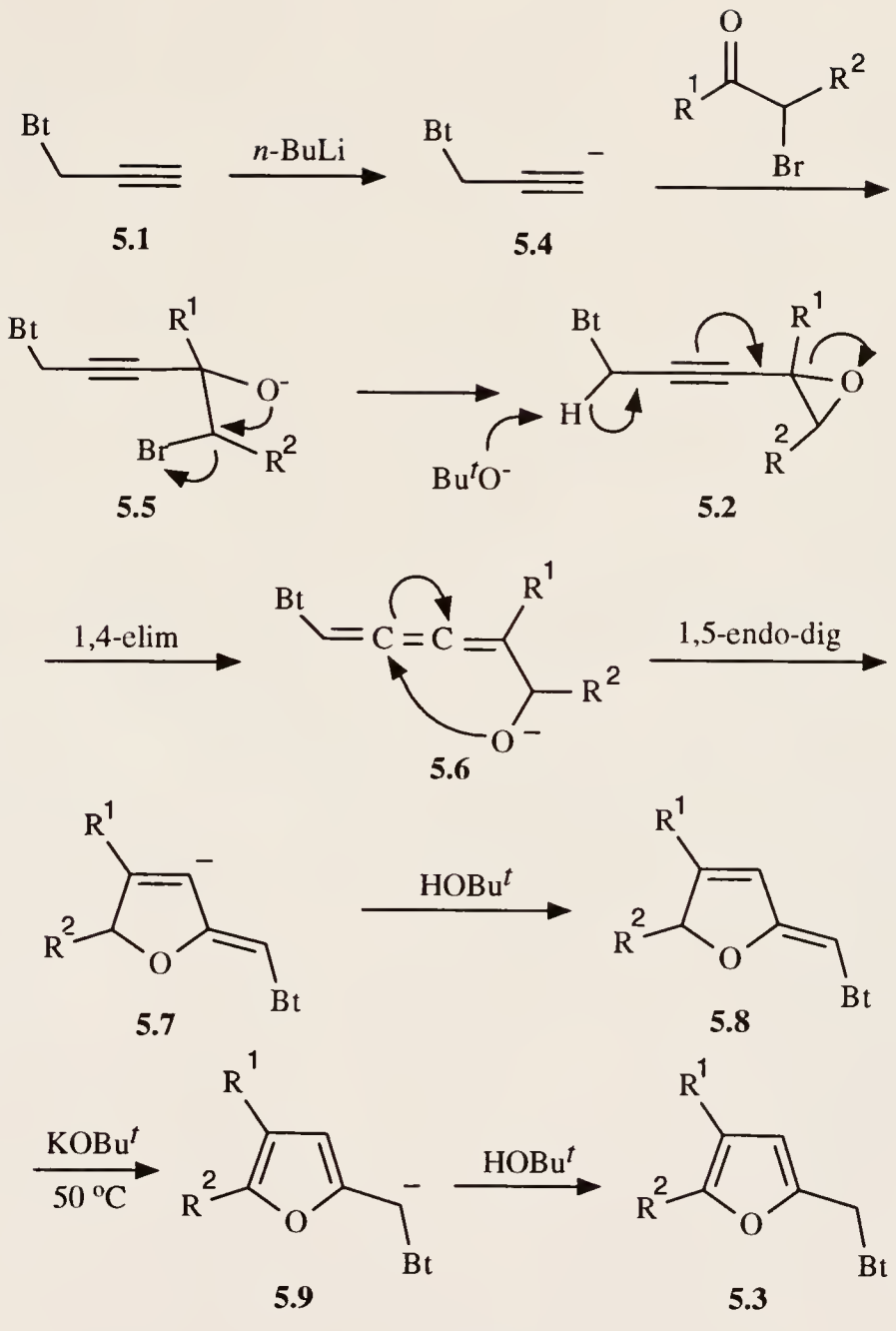


Scheme 5.1

In practice, it is not necessary to isolate the alkynyloxiranes **5.2**. Thus, a one-pot synthesis of 4- and 4,5-substituted 2-(benzotriazol-1-yl)methylfurans **5.3** is available (Scheme 5.1). 1-Propargylbenzotriazole (**5.1**) was treated with one equivalent of *n*-butyllithium at -78 °C for 1 h, followed by treatment with α-bromoketones for 4 h at the same temperature. A solution of $KOBu^t$ in $HOBu^t$ was added and the reaction mixtures were warmed to 50 °C overnight to give the products **5.3** in 51-61% yields (Table 5.1). The products **5.3** were characterized by ^1H and ^{13}C NMR spectra and elemental analyses (Tables 5.1, 5.2 and 5.3).

5.2.2 Mechanism of furan fing construction

The following mechanism is proposed based on experimental and literature evidence (Scheme 5.2). 1-Propargylbenzotriazole (**5.1**) was deprotonated on treatment with *n*-BuLi to generate anion **5.4** which attacks the carbonyl group of the α-bromoketone to yield adduct **5.5**. The oxygen anion of **5.5** intramolecularly displaced bromide to form epoxide **5.2** which is isolable. Since benzotriazole is electron withdrawing, the propargyl triple bond can readily rearrange to an allene under basic conditions [93JOC3038]. Therefore, $KOBu^t$ efficiently promoted 1,4-elimination of alkynyloxirane **5.2** to form cumulenyl alkoxide **5.6** which underwent 1,5-*endo-dig* cyclization to afford vinyl anion **5.7** followed by rapid protonation to give compound **5.8**. Intermediate **5.8**, (which could be isolated at room temperature as demonstrated for **5.8c**, R^1=Ph, R^2=CH_3, see experimental), rearranged upon heating with $KOBu^t$ to form **5.9** which was protonated to give 4- or 4,5-substituted 2-(benzotriazol-1-yl)methylfurans **5.3**.


Bt
n-BuLi
Bt
O
R1
R2
Br
5.1
5.4
Bt
R1
O-
Br
R2
5.5
ButO-
Bt
R1
H
O
R2
5.2
1,4-elim
Bt
C = C
R1
R2
O-
5.6
1,5-endo-dig
R1
R2
O
Bt
5.7
HOBut
R1
R2
O
Bt
5.8
KOBut
50 °C
R1
R2
O
Bt
5.9
HOBut
R1
R2
O
Bt
5.3

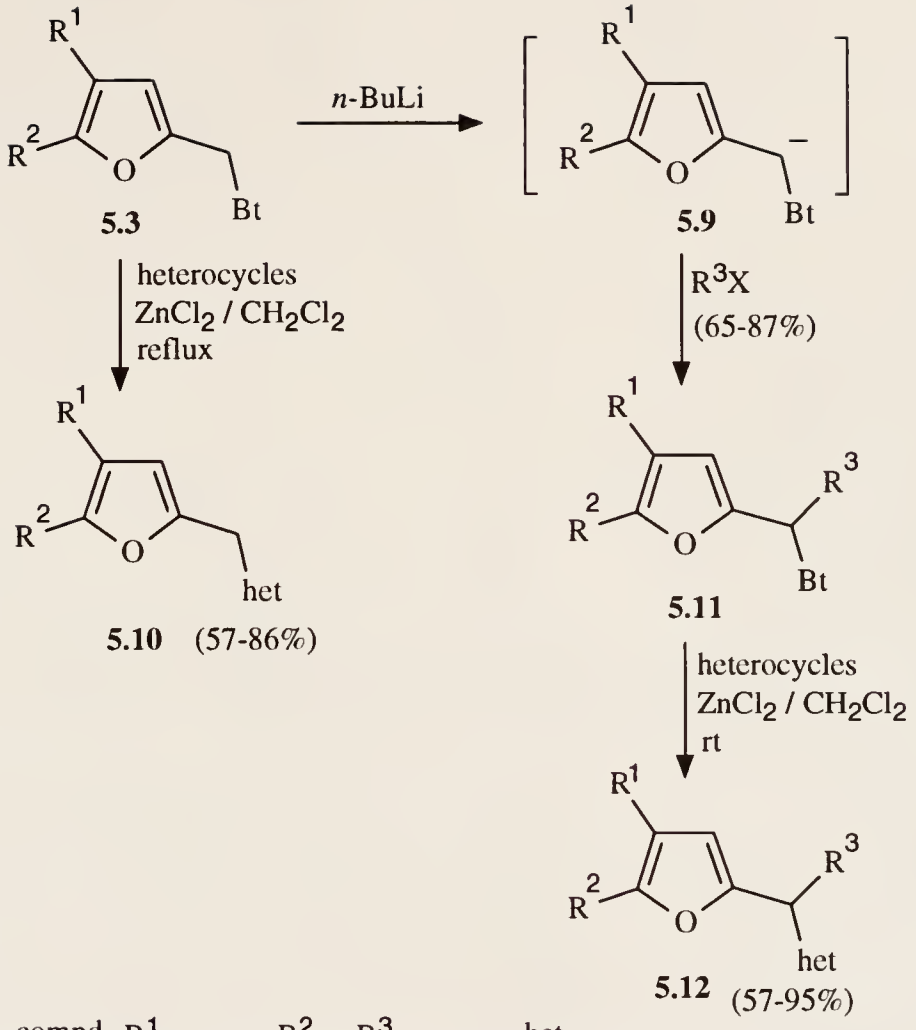
Scheme 5.2

5.2.3 Alkylation of 4- and 4,5-substituted 2-(benzotriazol-1-yl)methylfurans **5.3** and formation of 4- and 4,5-substituted 2-(α-heterocyclo)alkylfurans **5.10** and **5.12**

Benzotriazole has been extensively used in our laboratory as a synthetic auxiliary due to its electron withdrawing and good leaving group properties [93JOC4376]. Therefore, the benzotriazol-1-ylmethyl side chain of **5.3** can be elaborated by alkylation and substitution (Scheme 5.3). Compound **5.3** was treated with one equivalent of *n*-BuLi at -78 °C to generate anion **5.9** which then reacted with electrophiles such as benzyl bromide, *n*-butyl iodide, *i*-propyl iodide and methyl iodide to give the alkylated products **5.11** in 65-87% yields.

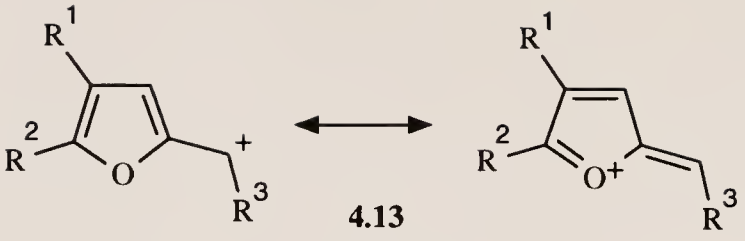
Compounds **5.3** and **5.11**, upon treatment with $ZnCl_2$ in CH_2Cl_2, underwent Friedel-Crafts type reactions with other heterocycles such as 2-methylfuran, 2-methylthiophene and *N*-methylindole to afford 4- and 4,5-substituted 2-(α-heterocyclo)alkylfurans **5.10** and **5.12** in good to excellent yields. The function of $ZnCl_2$ is to coordinate the nitrogen lone pair electrons of the benzotriazolyl group and assist benzotriazolyl group removal to generate the carbocation. Since the reaction involved the formation of carbocation **5.13** (Scheme 5.4), the R^3 and R^2 groups are essential for the reactivity of compounds **5.3** and **5.11**. Accordingly, the reactions of alkylated products **5.11** were carried out at room temperature. However, the reactions of compounds **5.3c,d** must be carried out under reflux in CH_2Cl_2. Compounds **5.3a,b** (R^3=R^2=H) did not undergo the reaction under reflux either in CH_2Cl_2 or in $CHCl_3$ and were recovered unchanged after such treatment. The mixture of **5.3a** and 2-methylthiophene, when heated under reflux in $CHCl_2CHCl_2$ in the presence of $ZnCl_2$, gave a complicated mixture.

As shown in scheme 5.3, the reactions took place at the 5-positions of 2-methylfuran and 2-methylthiophene and at the 3-position of *N*-methylindole. The



compd	R^1	R^2	R^3	het
10a	Ph	CH_3	-	5-methylfuran-2-yl
10b	Ph	CH_3	-	5-methylthiophen-2-yl
10c	CH_3	CH_3	-	5-methylthiophen-2-yl
10d	CH_3	CH_3	-	*N*-methylindol-3-yl
11a	Ph	H	$PhCH_2$	-
11b	2-naphthyl	H	*i*-Pr	-
11c	Ph	CH_3	*n*-Bu	-
11d	CH_3	CH_3	CH_3	-
12a	Ph	H	$PhCH_2$	5-methylthiophen-2-yl
12b	Ph	H	$PhCH_2$	*N*-methylindol-3-yl
12c	2-naphthyl	H	*i*-Pr	5-methylfuran-2-yl
12d	Ph	CH_3	*n*-Bu	5-methylfuran-2-yl
12e	CH_3	CH_3	CH_3	*N*-methylindol-3-yl

Scheme 5.3



4.13

Scheme 5.4

attached proton test (APT) spectra clearly showed quaternary carbon signals (δ=149.6-153.7) indicating C-2 of the 5-methylfuran-2-yl groups of compounds **5.10a**, **5.12c** and **5.12d**. Similarly, the C-2 signals of the 5-methylthiophen-2-yl groups of products **5.10b**, **5.10c** and **5.12a** appeared at δ=138.5-142.5. The ^{1}H singlets at δ=6.65-6.87, which are characteristic resonances of the α-H in 3-substituted indoles, and the quaternary carbon signals at δ=111.3-117.7 in the ^{1}H and APT NMR spectra of compounds **5.10d**, **5.12b** and **5.12e**, are strong evidence for the 3-substituted *N*-methylindole. Interestingly, the ^{1}H NMR spectra of compounds **5.12a** and **5.12b** clearly showed two sets of doublet of doublets between δ=3.22 and 3.47 ppm with large couplings (*J*=13.4-13.5 and 7.1-8.1 Hz) indicating the CH_2 diastereotopic signals are attached to chiral centers. Detailed assignments of the NMR spectra are listed in Tables 5.5 and 5.6.

All products are novel and are characterized by ^{1}H, ^{13}C and APT NMR spectra and combustion analyses (Tables 5.4, 5.5 and 5.6). Excess 2-methylfuran or 2-methylthiophene was used to minimize polymerization of compounds **5.3** and **5.11** and was removed by distillation at the completion of the reactions. $ZnCl_2$ was removed by washing with 2 N HCl solution and benzotriazole was extracted into the aqueous phase with 5% NaOH. The products were readily isolated by short column chromatography. Upon heating in air, products **5.10** and **5.12** were polymerized and their ^{1}H NMR spectra showed broad signals.

In conclusion, we have described a simple one-pot synthesis of 2,4- and 2,4,5-substituted furans **5.3** from the readily and commercially available starting materials 1-propargylbenzotriazole (**5.1**) and α-bromoketones. The benzotriazolyl group assisted the base-catalyzed isomerization of the intermediate alkynyloxiranes **5.2**, and therefore, 18-crown-6 was not required. In addition, since the benzotriazolyl group acts as either an electron withdrawing substituent or as a good leaving group, the benzotriazol-1-ylmethyl group of compounds **5.3** is readily elaborated by alkylation and substitution. A variety of 4- and 4,5-substituted 2-(α-heterocyclo)alkylfurans **5.10** and **5.12** were prepared in this manner.

5.3 Experimental

Melting points were determined on a bristoline hot-stage microscope and are uncorrected. NMR spectra were taken in $CDCl_3$ with TMS as an internal standard for ^1H (300 MHz) or $CDCl_3$ as an internal standard for ^{13}C (75 MHz). Assignments for ^{13}C NMR spectra in necessary cases were confirmed by APT experiments. Elemental analyses (C, H, N) were carried out within the department. Column chromatography was conducted over silica gel (230-400 mesh). All α-bromoketones and $ZnCl_2$ were used as purchased. 1-Propargylbenzotriazole (**5.1**) was prepared by the previously reported method [92LA843].

5.3.1 6-(Benzotriazol-1-yl)-2,3-epoxy-3-methyl-4-hexyne (**5.2d**)

To a stirred solution of 1-propargylbenzotriazole (**5.1**) (1.57 g, 10 mmol) in THF (30 mL) at -78 °C was added a solution of *n*-BuLi (5.5 mL, 2.0 M in

cyclohexane, 11 mmol). The mixture was stirred at this temperature for 1 h and 3-bromo-2-butanone (1.66 g, 11 mmol) in THF (5 mL) was added slowly. After stirring at -78 °C for 4 h, ether (100 mL) was added and the reaction mixture was washed with saturated NH_4Cl solution (3 x 100 mL) and dried ($MgSO_4$). Evaporation of the solvent gave a crude product which was purified by column chromatography using EtOAc/hexane (1:4) as the eluent to afford pure **5.2d** (1.82 g, 80%) as a white solid: mp 83-84 °C; ^1H NMR δ 8.05 (d, J = 8.4 Hz, 1 H, Bt), 7.69 (d, J = 8.3 Hz, 1 H, Bt), 7.50-7.55 (m, 1 H, Bt), 7.36-7.42 (m, 1 H, Bt), 5.48 (s, 2 H, CH_2), 3.21 (q, J = 5.5 Hz, 1 H, CH), 1.45 (s, 3 H, CH_3), 1.27 (d, J = 5.5 Hz, 3 H, CH_3); ^{13}C NMR δ 145.9 (Bt), 132.2 (Bt), 127.4 (Bt), 123.8 (Bt), 119.7 (Bt), 109.5 (Bt), 87.1 (C≡*C*), 73.1 (CH_2*C*≡C), 60.0 (CH), 50.1 (O*C*CH_3), 37.9 (CH_2), 17.5 (CH_3), 13.1 (CH_3). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.69; H, 5.77; N, 18.50. Found: C, 68.74; H, 5.77; N, 18.49.

5.3.2 Preparation of 4- and 4,5-Substituted 2-(α-benzotriazol-1-yl)methylfurans **5.3a-d**

A solution of *n*-BuLi (10.5 mL, 2.0 M in cyclohexane, 21 mmol) was added dropwise with stirring to a solution of 1-propargylbenzotriazole (**5.1**) (3.14 g, 20 mmol) in THF (100 mL) at -78 °C. The mixture was stirred at this temperature for 1 h and α-bromoketone (21 mmol) in THF (10 mL) was added slowly. The mixture was stirred for 4 h and $KOBu^t$ (2.24 g, 20 mmol) in $HOBu^t$ (20 mL) was added. The reaction solution was allowed to warm to room temperature and then heated at 50 °C overnight. H_2O (100 mL) and EtOAc (100 mL) were added. The organic phase was washed with saturated NH_4Cl solution (3 X 100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an oil which was subjected to either

recrystallization or column chromatography to afford the product **3** (Table 5.1).

5.3.3 2-(Benzotriazol-1-yl)methylene-4-phenyl-5-methyl-2,5-dihydrofuran (**5.8c**)

To a stirred solution of 1-propargylbenzotriazole (**5.1**) in THF (30 mL) at -78 °C was addd a solution of *n*-BuLi (5.5 mL, 2.0 M in cyclohexane, 11 mmol). After 1 h, 2-bromopropiophenone (2.60 g, 90%, 11 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 4 h. KOBu^t (1.12 g, 10 mmol) in HOBu^t (10 mL) was added at -78 °C and the reaction solution was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl solution (100 mL), extracted with EtOAc, washed with saturated NH_4Cl solution (3 x 100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil which was subjected to column chromatography to afford pure **8c** (1.50 g, 52%) as a yellow oil: ^{1}H NMR δ 8.05 (d, *J* = 8.4 Hz, 1 H, Bt), 7.67 (d, *J* = 8.3 Hz, 1 H, Bt), 7.32-7.50 (m, 7 H, Bt and Ph overlapped), 6.64 (s, 1 H, C=CH), 6.58 (s, 1 H, C=CH), 5.82 (q, *J* = 6.5 Hz, 1 H, CH), 1.51 (d, *J* = 6.5 Hz, 3 H, CH_3); ^{13}C NMR δ 156.2 (*C*=CH), 151.5 (*C*=CH), 145.3 (Bt), 132.8 (Bt), 131.0 (Ph), 129.5 (Ph), 128.8 (2C, Ph), 126.8 (Bt), 126.4 (2C, Ph), 123.6 (Bt), 119.5 (Bt), 117.0 (C=*C*H), 111.7 (Bt), 93.9 (C=*C*H), 85.7 (CH), 20.4 (CH_3). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.71; H, 5.23; N, 14.53. Found: C, 75.09; H, 5.32; N, 14.40.

5.3.4 Alkylation of 4- and 4,5-Substituted 2-(α-benzotriazol-1-yl)methylfurans **5.3**

To a solution of compound **5.3** (5 mmol) in THF (50 mL) was added a solution of n-BuLi (2.75 mL, 2.0 M in cyclohexane, 5.5 mmol) dropwise with stirring

at -78 °C. The mixture was stirred for 1 h and alkyl halide (5.5 mmol) was added. The mixture was stirred at -78 °C for 5 h and was then allowed to warm to room temperature. H_2O (100 mL) and Et_2O (100 mL) were added and the organic phase was washed with NaCl solution (3 X 100 mL) and dried ($MgSO_4$). Et_2O was evaporated under reduced pressure to give an oil which was purified by column chromatography to yield the product **5.11** (Table 5.1).

5.3.5 Formation of 4- and 4,5-Substituted 2-(α-heterocyclo)alkylfurans **5.10** and **5.12**

A mixture of 4- or 4,5-substituted 2-(α-benzotriazol-1-yl)alkylfuran **5.3** or **5.11** (2 mmol), $ZnCl_2$ (2 mmol) and heterocycle (20 mmol for 2-methylfuran and 2-methylthiophene and 2 mmol for *N*-methylindole) in CH_2Cl_2 (50 mL) was stirred at room temperature (for **5.3c** and **5.3d** under reflux) under nitrogen overnight. The reaction was washed with HCl solution (2 N, 50 mL), NaOH solution (5%, 3 X 50 mL) and dried ($MgSO_4$). CH_2Cl_2 was removed under reduced pressure to give a residue. The product **5.10** or **5.12** was separated from the residue by column chromatography (Table 5.4).

Table **5.1** Synthesis of 4- and 4,5-Substituted 2-(α-Benzotriazol-1-ylalkyl)furans **5.3** and **5.11**

compd	yield (%)	mp (°C)	appearance	molecular formula	found			calcd		
					C	H	N	C	H	N
5.3a	61	121-122	powder[a]	$C_{17}H_{13}N_3O$	74.42	4.81	15.18	74.17	4.76	15.26
5.3b	51	152-153	powder[a]	$C_{21}H_{15}N_3O$	77.85	4.68	12.83	77.52	4.65	12.91
5.3c	53	98-99	powder[b]	$C_{18}H_{15}N_3O$	75.09	5.29	14.16	74.72	5.23	14.52
5.3d	55	129-130	needles[c]	$C_{13}H_{13}N_3O$	68.97	5.83	18.64	68.69	5.77	18.50
5.11a	87	-	oil[b]	$C_{24}H_{19}N_3O$	78.95	5.22	11.25	78.88	5.24	11.50
5.11b	78	65-67	powder[b]	$C_{24}H_{21}N_3O$	78.76	5.79	11.16	78.45	5.76	11.44
5.11c	65	-	oil[b]	$C_{22}H_{23}N_3O$	76.49	6.76	12.10	76.48	6.72	12.17
5.11d	82	-	oil[b]	$C_{14}H_{15}N_3O$	69.64	6.33	17.45	69.67	6.27	17.42

[a] Recrystallized from EtOH.
[b] Column chromatography (EtOAc / hexane 1:1).
[c] Recrystallized from EtOAc / hexane.

Table **5.2** ^{1}H NMR Data of Compounds **5.3** and **5.1** ($CDCl_3$), δ (ppm), *J* (Hz)

compd	Bt				H-3	CH	R^1	R^2	R^3
	H-4	H-5	H-6	H-7	(furan)	or CH_2			
5.3a	8.03 (d, 8.4)	7.22-7.46 (m)[a]	7.22-7.46 (m)[a]	7.57 (d, 8.3)	6.71 (s)	5.79 (2H, s)	7.22-7.46 (5H, m)[a]	7.61 (1H, s)	-
5.3b	8.06 (d, 8.3)	7.32-7.51 (m)[a]	7.32-7.51 (m)[a]	7.59 (d, 8.3)	6.82 (s)	5.83 (2H, s)	7.76-7.82 (4H, m), 7.32-7.51 (3H, m)[a]	7.73 (1H, s)	-
5.3c	8.02 (d, 8.3)	7.20-7.35 (m)[a]	7.41 (dd, 8.2 and 7.3)	7.60 (d, 8.2)	6.54 (s)	5.74 (2H, s)	7.20-7.35 (5H, m)[a]	2.32 (3H, s)	-
5.3d	8.03 (d, 8.3)	7.33 (dd, 8.3 and 7.4)	7.44 (dd, 8.1 and 7.4)	7.57 (d, 8.1)	6.20 (s)	5.70 (2H, s)	2.12 (3H, s)	1.87 (3H, s)	-
5.11a	7.98 (d, 8.3)	6.98-7.37 (m)[a]	6.98-7.37 (m)[a]	7.44 (d, 8.3)	6.70 (s)	6.22 (1H, t, 7.4)	6.98-7.37 (5H, m)[a]	7.60 (1H, s)	6.98-7.37 (5H, m),[a] 3.83 (2H, d, 7.3)
5.11b	8.07 (d, 8.3)	7.31-7.54 (m)[a]	7.31-7.54 (m)[a]	7.74-7.85 (m)[a]	6.91 (s)	5.69 (1H, d, 10.6)	7.74-7.85 (4H, m),[a] 7.31-7.54 (3H, m)[a]	7.72 (1H, s)	3.11-3.19 (1H, m), 1.13 (3H, d, 6.6), 0.79 (3H, d, 6.6)
5.11c	8.07 (d, 8.2)	7.23-7.44 (m)[a]	7.23-7.44 (m)[a]	7.59 (d, 8.3)	6.55 (s)	6.03 (1H, dd, 9.0 and 6.8)	7.23-7.44 (5H, m)[a]	2.36 (3H, s)	2.51-2.50 (2H, m), 1.22-1.40 (4H, m), 0.86 (3H, t, 7.3)
5.11d	8.03 (d, 8.3)	7.28-7.45 (m)	7.28-7.45 (m)	7.28-7.45 (m)	6.19 (s)	6.17 (1H, q, 7.2)	2.10 (3H, s)	1.90 (3H, s)	2.01 (3H, d, 7.2)

[a] Overlapped with other aromatic signals.

Table **5.3** ^{13}C NMR of Compounds **5.3** and **5.11** ($CDCl_3$), δ (ppm)

compd	Bt						Furan				CH_2 or CH	R^1	R^2	R^3
	C-4	C-5	C-6	C-7	C_{3a}	C_{7a}	C-2	C-3	C-4	C-5				
5.3a	119.8	127.4	123.9	109.6	146.0	132.6	148.7	108.7	127.3	138.7	44.9	131.4, 128.7, 127.2, 125.6	-	-
5.3b	119.9	127.6	124.0	109.6	146.1	132.7	149.0	108.8	127.5	139.2	45.1	133.5, 132.5, 128.9, 128.5, 127.7, 127.6, 126.4, 125.8	-	-
5.3c	119.6	127.2	123.7	109.6	145.9	132.5	148.4	110.9	121.7	145.2	44.8	133.0, 128.3, 127.1, 126.3	12.8	-
5.3d	119.7	127.2	123.7	109.8	146.1	132.6	148.3	112.9	114.9	144.4	45.2	11.2	9.6	-
5.11a	119.7	127.1	123.6	109.6	145.8	132.3	151.5	107.8	126.8	138.2	58.7	135.8, 128.5, 128.3, 127.1	-	131.4, 128.4, 127.1, 127.0, 38.4
5.11b	120.0	127.3	123.8	110.3	146.2	132.4	152.0	108.5	127.2	138.5	64.2	133.5, 132.5, 129.0, 128.4, 127.7, 127.6, 126.3, 125.7	-	31.2, 20.2, 19.5
5.11c	120.0	127.1	123.7	110.3	146.4	132.1	149.0	109.6	121.6	148.0	57.7	133.4, 128.5, 127.3, 126.5	13.0	31.5, 28.2, 22.0, 13.7
5.11d	119.7	126.9	123.6	110.3	146.1	131.8	148.3	111.1	114.6	147.7	53.0	11.6	9.6	18.2

Table **5.4** Preparation of 4- and 4,5-Substituted 2-(α-Heterocycloalkyl)furans **5.10** and **5.12**

entry[a]	reactant	heterocycle	product[b]	yield (%)	molecular formular	found (calcd)		
						C	H	N
1	**3c**	2-methylfuran	**5.10a**	57	$C_{17}H_{16}O_2$	80.88(80.92)	6.49(6.40)	
2	**3c**	2-methylthiophene	**5.10b**	86	$C_{17}H_{16}OS$	75.99(76.09)	6.01(6.01)	
3	**3d**	2-methylthiophene	**5.10c**	67	$C_{12}H_{14}OS$	70.09(69.88)	6.84(6.85)	
4	**3d**	*N*-methylindole	**5.10d**	63	$C_{16}H_{17}NO$	80.61(80.29)	7.52(7.16)	5.81(5.86)
5	**11a**	2-methylthiophene	**5.12a**	61	$C_{23}H_{20}OS$	80.09(80.20)	5.84(5.86)	
6	**11a**	*N*-methylindole	**5.12b**	57	$C_{27}H_{23}NO$	85.99(85.90)	6.12(6.15)	3.54(3.71)
7	**11b**	2-methylfuran	**5.12c**	68	$C_{23}H_{22}O$	83.34(83.60)	6.81(6.72)	
8	**11c**	2-methylfuran	**5.12d**	95	$C_{21}H_{24}O_2$	81.72(81.77)	7.97(7.85)	
9	**11d**	*N*-methylindole	**5.12e**	79	$C_{17}H_{19}NO$	80.93(80.59)	7.67(7.56)	5.45(5.53)

[a] Reactions (1-4) were carred out under reflux in CH_2Cl_2 and reactions (5-9) were carried out at room temperature.

[b] All products were oily and separated by column chromatography (CH_2Cl_2 / hexane 1:4).

Table **5.5** ^{1}H NMR Data of Compounds **5.10** and **5.12** ($CDCl_3$), δ (ppm), *J* (Hz)

compd	H-3 (furan)	heterocycle	CH or CH_2	R^1	R^2	R^3
5.10a	6.12 (s)	5.92 (1H, d, 2.7), 5.79-5.81 (1H, m), 2.32 (3H, s)	3.84 (2H, s)	7.25-7.30 (4H, m), 7.12-7.17 (1H, m)	2.18 (3H, s)	-
5.10b	6.12 (s)	6.60 (1H, d, 3.4), 6.12-6.50 (1H, m), 2.34 (3H, s)	3.97 (2H, s)	7.25-7.29 (4H, m), 7.12-7.16 (1H, m)	2.32 (3H, s)	-
5.10c	5.83 (s)	6.63 (1H, d, 3.3), 6.54-6.55 (1H, m), 2.41 (3H, s)	3.98 (2H, s)	2.45 (3H, s)	1.88 (3H, s)	-
5.10d	5.76 (s)	7.57 (1H, d, 7.8), 7.17-7.27 (2H, m), 7.05-7.11 (1H, m), 6.87 (1H, s), 3.69 (3H, s)	4.00 (2H, s)	2.15 (3H, s)	1.85 (3H, s)	-
5.12a	6.35 (s)	6.57 (1H, d, 4.0), 6.49-6.51 (1H, m), 2.39 (3H, s)	4.43 (1H, t, 7.8)	7.11-7.33 (5H, m)[a]	7.61 (1H, s)	7.40 (2H, d, 7.3), 7.11-7.33 (1H, m),[a] 7.05 (2H, d, 7.0), 3.44 (1H, dd, 13.5 and 7.8), 3.22 (1H, dd, 13.5 and 7.8)
5.12b	6.32 (s)	7.58 (1H, d, 8.6), 7.03-7.30 (3H, m),[a] 6.82 (1H, s), 3.62 (3H, s)	4.52 (1H, t, 7.6)	7.03-7.30 (5H, m)[a]	7.60 (1H, s)	7.38 (2H, d, 8.3), 7.03-7.30 (3H, m),[a] 3.47 (1H, dd, 13.4 and 8.1), 3.37 (1H, dd, 13.4 and 7.1)
5.12c	6.56 (s)	7.58 (1H, d, 3.0), 5.88-5.90 (1H, m), 2.27 (3H, s)	3.79 (1H, d, 8.1)	7.87 (1H, s), 7.76-7.79 (3H, m), 7.57 (1H, d, 8.5), 7.36-7.46 (2H, m)	7.72 (1H, s)	2.36-2.43 (1H, m), 0.95 (6H, d, 6.8)
5.12d	6.18 (s)	5.97 (1H, d, 2.9), 5.86-5.87 (1H, m), 2.40 (3H, s)	3.94 (1H, t, 7.6)	7.31-7.38 (4H, m), 7.17-7.23 (1H, m)	2.25 (3H, s)	1.94-2.02 (2H, m), 1.29-1.33 (4H, m), 0.89 (3H, t, 6.7)
5.12e	5.65 (s)	7.45 (1H, d, 7.9), 7.01-7.09 (2H, m), 6.89-6.95 (1H, m), 6.65 (1H, s), 3.45 (3H, s)	4.21 (1H, q, 7.2)	2.01 (3H, s)	1.74 (3H, s)	1.53 (3H, d, 7.2)

[a] Overlapped signals.

Table **5.6** ^{13}C NMR Data of Compounds **5.10** and **5.12** ($CDCl_3$), δ (ppm)

compd	furan				heterocycle	CH or CH_2	R^1	R^2	R^3
	C-2	C-3	C-4	C-5					
5.10a	151.0	107.7	121.5	149.5	149.6, 146.5, 107.1, 106.1, 13.0	27.4	134.3, 128.4, 127.3, 126.1	13.5	-
5.10b	151.5	107.6	121.4	146.5	138.5, 138.0, 125.3, 124.7, 15.3	28.9	134.3, 128.4, 127.3, 126.1	13.0	-
5.10c	150.6	109.2	114.4	146.1	138.6, 138.3, 125.0, 124.7, 15.3	28.9	11.3	9.9	-
5.10d	151.8	108.7	114.3	145.5	137.0, 127.7, 127.0, 121.5, 119.2, 118.7, 111.3, 109.1, 32.5	24.2	11.3	9.9	-
5.12a	157.4	105.3	126.9	137.1	142.5, 139.1, 126.2, 124.5, 15.3	42.8	138.3, 128.9, 128.6, 125.6	-	132.5, 128.1, 126.8, 124.6, 42.0
5.12b	158.4	105.1	126.8	136.8	137.1, 126.8, 126.0, 121.5, 119.3, 118.9, 115.0, 109.3, 38.9	32.6	140.1, 128.9, 128.6, 128.1	-	132.7, 128.2, 126.6, 125.6, 40.7
5.12c	156.5	107.1	126.8	137.3	152.6, 150.7, 106.0, 105.5, 13.6	46.4	133.7, 132.4, 130.1, 128.3, 127.7, 127.6, 126.2, 125.5, 124.3, 123.7	-	31.8, 20.7
5.12d	153.8	106.8	121.2	150.6	153.7, 146.1, 106.2, 105.9, 13.1	38.9	134.4, 128.4, 127.3, 126.0	13.6	32.7, 29.6, 22.5, 14.0
5.12e	156.3	107.5	114.0	145.3	137.1, 126.9, 125.7, 121.3, 119.5, 118.5, 117.7, 109.1, 30.6	32.3	11.3	9.9	20.3

CHAPTER VI
FACILE SYNTHESIS OF 2-SUBSTITUTED INDOLES AND INDOLO[3,2-b]CARBAZOLES FROM 2-(BENZOTRIAZOL-1-YLMETHYL)INDOLE

6.1 Introduction

2-Substituted indoles are pharmacologically important substances and are precursors for a wide variety of alkaloids [83MI1] such as vindoline, vindorosine [87JOC347], ellipticine [89JOC3084], etc. Perhaps, the most general approach to 2-substituted indoles involves 2-lithiation of indoles, promoted by directing groups such as 1-benzenesulfonyl [73JOC3324], 1-lithiocarboxylate [85TL5935], 1-(dimethylamino)methyl [89H849], 1-*tert*-butylcarbamoyl [91S1079] and 1-(2-oxazolinyl) [92H173], followed by reaction with a wide range of electrophiles. Recently, several methods for the preparation of 2-substituted indoles were developed which involve elaboration of 2-methylindole, eg. α-bromination [82S926, 85S188 and 92S743] followed by substitution of the bromine atom or α-deprotonation followed by alkylation of protected indoles [89TL2509 and 92S648]. However, protection of the indole 3-position is a problem associated with many of these methods. In our previous work, we described a useful methodology in which a variety of 2-substituted indoles were afforded by 2-alkyl lithiation of 2-alkylindoles activated by carbon dioxide and subsequent electrophilic substitution [86JA6808].

Indolo[3,2-b]carbazoles have gained significant importance pharmacologically since they inhibit the specific binding of toxic dioxins which give rise to thymic

atrophy, hyperkeratosis and chloracne in liver cytosol [86MI1673]. A number of synthetic methods for the preparation of 5,11-dihydroindolo[3,2-b]carbazoles have been described: (i) vapor phase catalytic cyclodehydrogenation of *N,N'*-diphenyl-*p*-phenylenediamine [61JOC1509]; (ii) Fischer indolization of cyclohexane-1,4-dione bisphenylhydrazone [63JCS3097]; (iii) condensation of indole and formaldehyde in the presence of air and sensitizers [70T3353]; (iv) polymerization of indole with *p*-toluenesulfonic acid in Dowtherm A [88JCS(P1)2387]; and (v) transformation of 4,9-dihydropyrano[3,4-b]indol-1(3*H*)-ones in the presence of mineral acids [89AP451]. However, all of these methods suffer from low yields and require vigorous reaction conditions. No general method for the conversion of 2-substituted indoles to indolo[3,2-b]carbazoles has been reported previously.

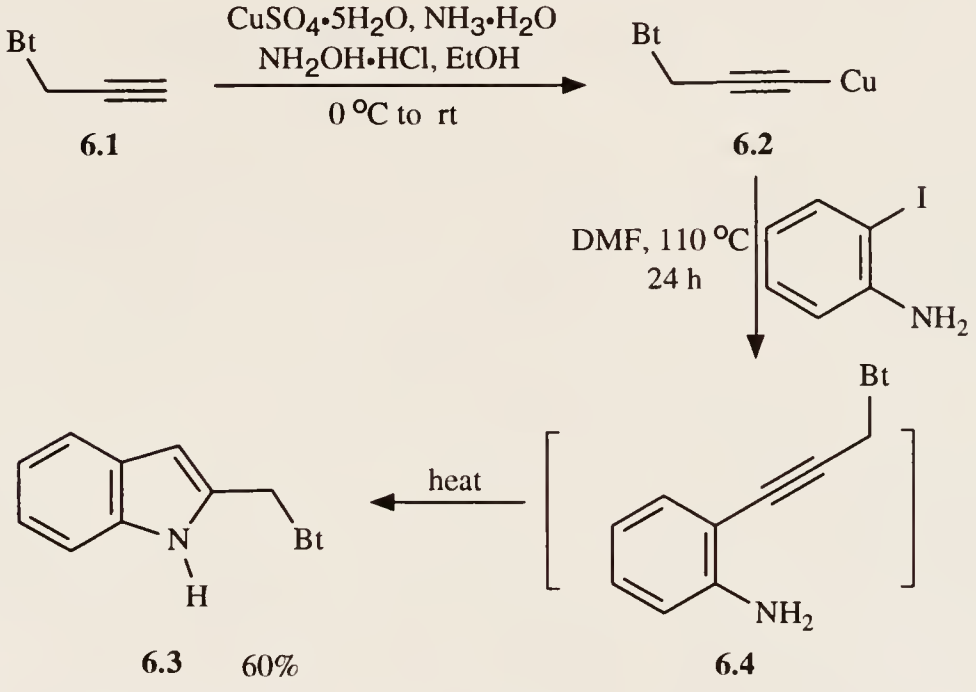
We now present a convenient method for the synthesis of 2-substituted indoles from 1-propargylbenzotriazole and *o*-iodoaniline involving alkylation and subsequent displacement of the benzotriazole moiety and a general method for the preparation of 6,12-dihydroindolo[3,2-b]carbazoles and 5,11-dihydroindolo[3,2-b]carbazoles.

6.2 Results and Discussion

6.2.1 Preparation of 2-(benzotriazol-1-ylmethyl)indole (**6.3**)

Castro and coworkers [66JOC4071] developed an efficient method for the formation of 2-alkyl- and 2-aryl- indoles from a variety of cupric acetylides and *o*-iodoaniline derivatives. However, the possibility of employing this method for the preparation of functionalized 2-alkylindoles had not been exploited until the present work. We have now prepared 2-(benzotriazol-1-ylmethyl)indole (**6.3**) (Scheme 6.1)

which contains a side chain methylene group that can be further elaborated as the benzotriazolyl group acts as both an activator for deprotonation and a good leaving group, as has been demonstrated extensively in our laboratory [91T2683].

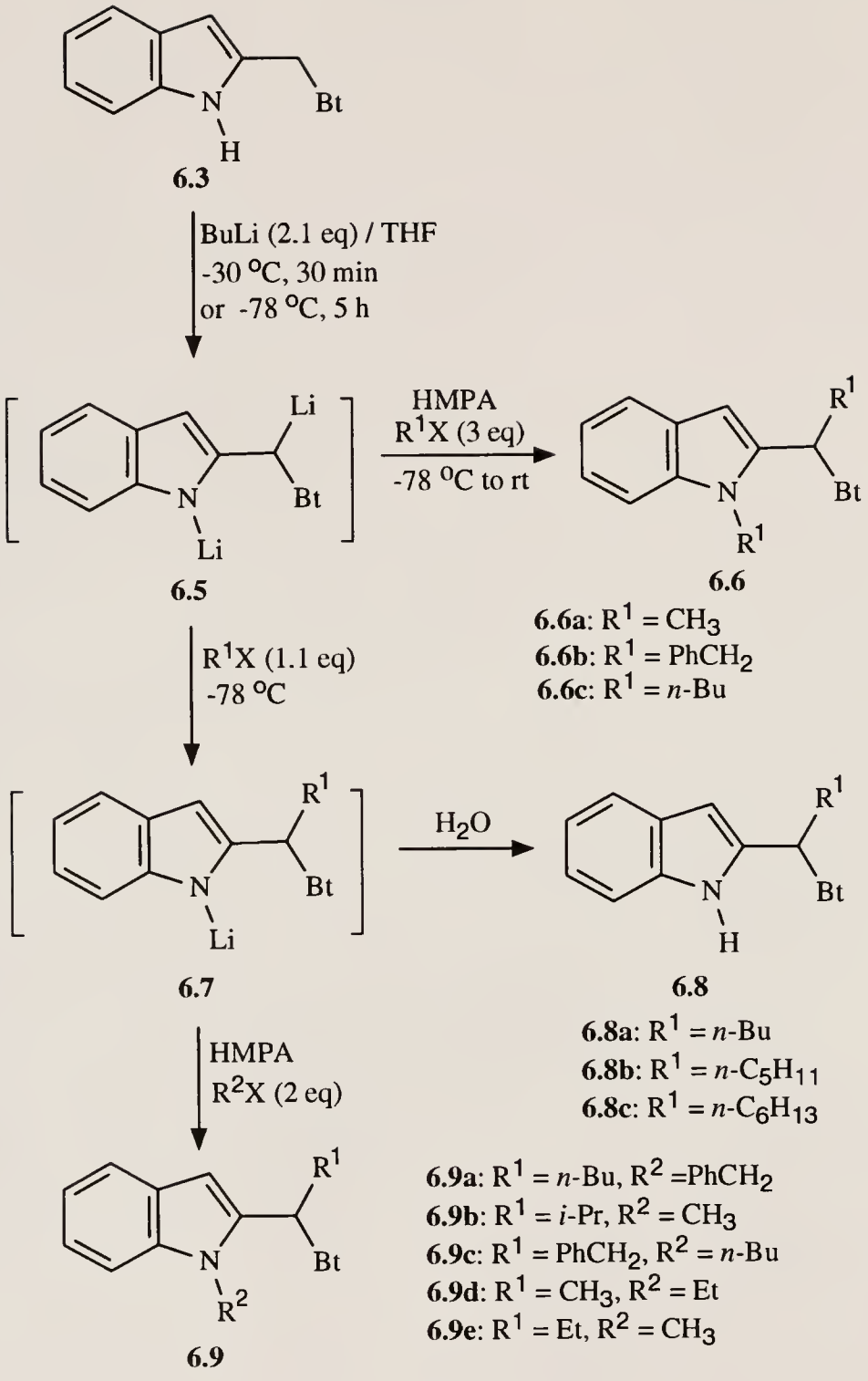


Bt = benzotriazol-1-yl

Scheme 6.1

6.2.2 Deprotonation of 2-(benzotriazol-1-ylmethyl)indole (**6.3**) and reaction of the lithiated derivatives with electrophiles

Compound **6.3** was treated with 2.1 equivalents of *n*-butyllithium in THF at -30 °C for 30 min or at -78 °C for 5 h to generate the dianion **6.5** which was then reacted with 1.1 equivalents of alkyl halide to form anions **6.7**. These anions **6.7** were quenched with water to afford the alkylated indoles **6.8** in high yield.


Bt
N
H
6.3
BuLi (2.1 eq) / THF
-30 °C, 30 min
or -78 °C, 5 h
Li
Bt
N
Li
6.5
HMPA
R1X (3 eq)
-78 °C to rt
R1
Bt
N
R1
6.6
6.6a: R1 = CH3
6.6b: R1 = PhCH2
6.6c: R1 = n-Bu
R1X (1.1 eq)
-78 °C
R1
Bt
N
Li
6.7
H2O
R1
Bt
N
H
6.8
6.8a: R1 = n-Bu
6.8b: R1 = n-C5H11
6.8c: R1 = n-C6H13
HMPA
R2X (2 eq)
R1
Bt
N
R2
6.9
6.9a: R1 = n-Bu, R2 =PhCH2
6.9b: R1 = i-Pr, R2 = CH3
6.9c: R1 = PhCH2, R2 = n-Bu
6.9d: R1 = CH3, R2 = Et
6.9e: R1 = Et, R2 = CH3

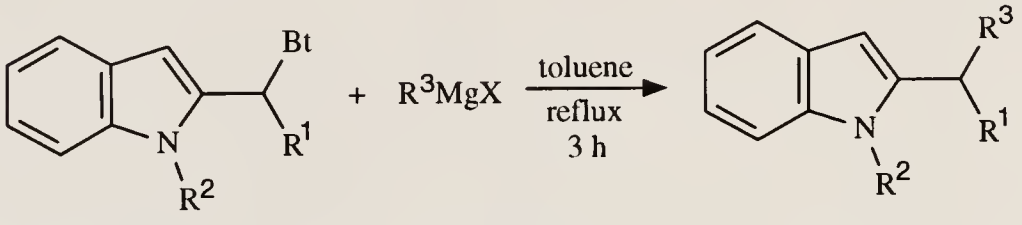
Scheme 6.2

The *N*-alkylation of indole has been well studied [67TL3771, 72S566 and 73JCS(P1)499]. The general method involves *N*-metalation followed by substitution with alkyl halides. The reaction solvents are especially important and the site-specific *N*-alkylation is favored by dipolar aprotic solvents such as HMPA and DMSO [72S566 and 73JCS(P1)499]. When anions **6.7** were quenched with excess halide ($PhCH_2Br$ or *n*-BuI) in THF at room temperature for 24 hours, only trace amounts of *N*-alkylated products were detected by ^1H NMR. Presumably, the nucleophilicities of indole lithium salts are weaker than those of indole sodium salts [67TL3771]. However, when HMPA was added to comprise 50% of the total solvent, high yields of *N*-alkylated products were obtained. Thus, after the generation of dianion **6.5** in THF, an equal amount of HMPA as solvent and three equivalents of alkyl halide were added to the reaction mixture at -30 °C. The solution was allowed to warm to room temperature overnight to give the dialkylated products **6.6** in good yield.

Alternatively, the dianion **6.5** was first reacted with 1.1 equivalents of alkyl halide at -78 °C in THF for several hours. Two equivalents of a second alkyl halide and an amount of HMPA equal to that of THF were added at -30 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight to form the regiospecifically 1,2-dialkylated products **6.9**. A variety of mono- and dialkylated compounds were prepared similarly (Scheme 6.2). The structures of products **6.6, 6.8** and **6.9** were confirmed by ^1H, ^{13}C, and APT NMR spectra (Tables 6.4 and 6.5) and elemental analyses (Table 6.1).

6.2.3 Substitution of 2-(1-benzotriazol-1-ylalkyl)indoles **6.6** and **6.9** with Grignard reagents

It is well-known that the benzotriazole moiety acts as a good leaving group in reactions with Grignard reagents [91T2683]. Therefore, reaction of compounds **6.6** and **6.9** with aryl or alkyl magnesium halides in refluxing toluene for 3 hours gave the corresponding products **6.10** in good yield (Scheme 6.3). Following this procedure, a wide range of 2-alkylindoles **6.10** was obtained (Table 6.2).



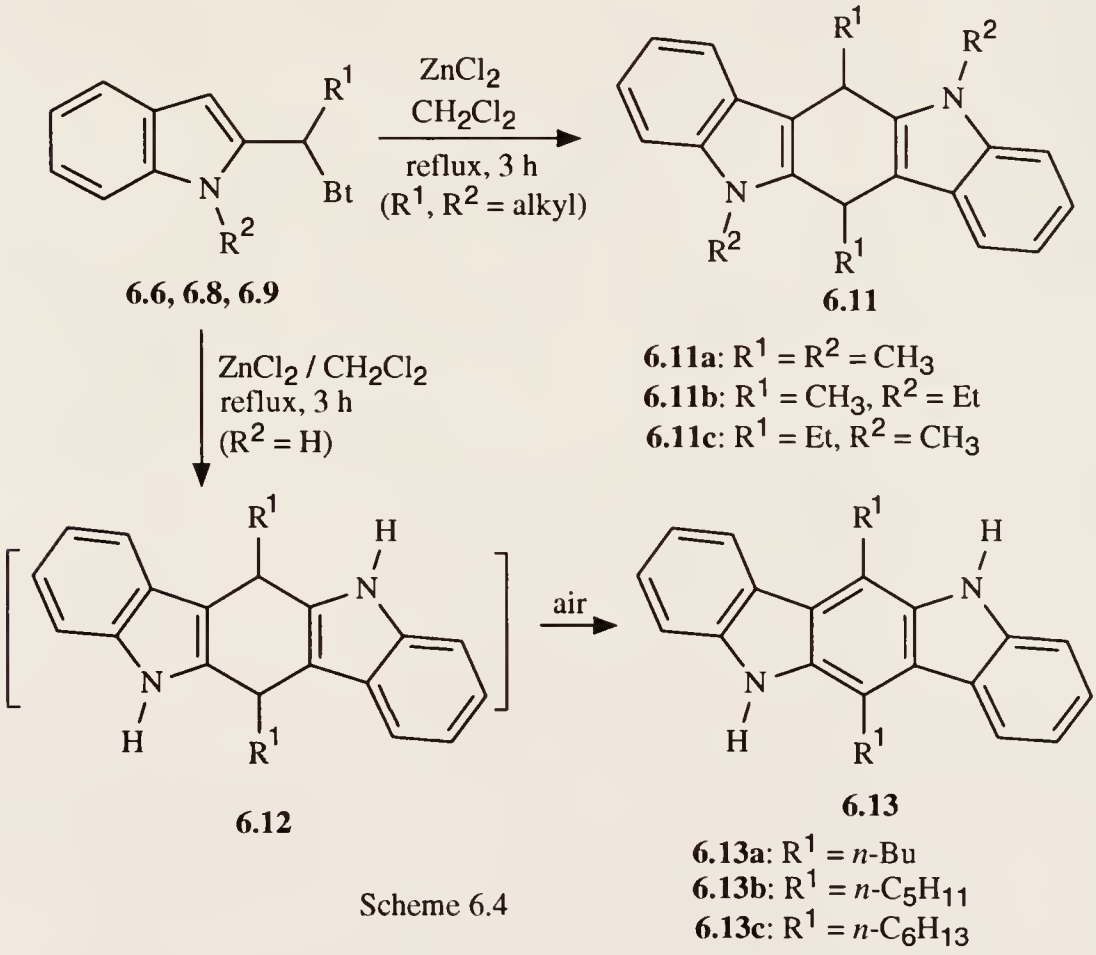
6.6, 6.9 **6.10**

Scheme 6.3

The structures of compounds **6.10** were elucidated by ^{1}H, ^{13}C and APT NMR spectra (Tables 6.6 and 6.7) and combustion analyses (Table 6.2). Interestingly, the ^{1}H NMR spectra of compounds **6.10b** and **6.10f** showed typical diastereotopic CH_2 patterns. The presence of two doublet of doublet signals at δ 3.06-3.48 ppm in each compound indicated that the CH_2 protons were attached to the chiral centers. The two doublets (δ 4.90, 5.12) with larger coupling constants (J = 17.1 Hz) in the ^{1}H NMR spectrum of compound **6.10b** showed strong through space interaction between the *N*-$\underline{CH_2}$Ph and the chiral center. Moreover, the second CH_2 protons in the *N*-butyl chain of compound **6.10f** resonated at greatly different fields (δ 1.26-1.41 ppm and 0.81-1.06 ppm respectively), indicating a short distance between the *N*-$CH_2\underline{CH_2}CH_2CH_3$ and the chiral center. The detailed assignments of the ^{1}H and ^{13}C NMR signals are given in Tables 6.6 and 6.7.

6.2.4 Dimerization and dehydrogenation

It has been previously reported that Lewis acids readily assist the formation of the benzotriazolyl anion and the corresponding carbocations from benzotriazole adducts. Such carbocations are then available for reaction with nucleophiles [91S868]. Therefore, compounds **6.6, 6.8** and **6.9** can act not only as nucleophiles due



Scheme 6.4

to the unoccupied 3-position of the indole ring, but also as carbocations with the assistance of Lewis acids. Hence, treatment of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)-indoles **6.6** and **6.9** with zinc chloride in refluxing methylene chloride yielded

6,12-dihydroindolo[3,2-b]carbazoles **6.11** which were relatively stable in air. No dehydrogenated product was detected by ^{1}H NMR spectroscopy. When compounds **6.8** were refluxed with zinc chloride in methylene chloride for 3 hours, dimeric intermediates **6.12** were formed which rapidly dehydrogenated in air to give 6,12-di-(*n*-alkyl)-5,11-dihydroindolo[3,2-b]carbazoles **6.13** (Scheme 6.4). Surprisingly, under similar reaction conditions, 2-(benzotriazol-1-ylmethyl)indole (**6.3**) did not undergo dimerization in either CH_2Cl_2 or $CHCl_3$. This indicates that the alkyl group of **6.8** efficiently stabilizes the cation and lowers the activation energy of the carbocation formation.

In summary, 2-(benzotriazol-1-ylmethyl)indole (**6.3**), derived from 1-propargylbenzotriazole cupric salt (**6.2**) and *o*-iodoaniline (Scheme 6.1) [66JOC4071], was treated with *n*-butyllithium to generate anion **6.5** which was subsequently trapped by electrophiles to give 2-(1-benzotriazol-1-ylalkyl)indoles **6.8** in high yield (Scheme 6.2). Compounds **6.8** underwent dimerization under the action of a Lewis acid, followed by dehydrogenation in air to afford 6,12-dialkyl-5,11-dihydroindolo[3,2-b]carbazoles **6.13** in good yield (Scheme 6.4). The treatment of **6.3** with two equivalents of *n*-butyllithium followed by quenching with three equivalents of alkyl halide using HMPA as the solvent gave *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indoles **6.6**. Reaction of dianion **6.5** sequentially with two different halides afforded compounds of type **6.9**. Under similar reaction conditions, **6.6** and **6.9** were converted to 6,12-dihydroindolo[3,2-b]carbazoles **6.11**. The benzotriazolyl group of compounds **6.6** and **6.9** was conveniently displaced by Grignard reagents to give 2-alkylindoles **6.10** in good yield. The reaction of *N*-alkyl--2-(1-benzotriazol-1-ylalkyl)indoles **6.6** and **6.9** with Grignard reagents provides a convenient route to a variety of 2-alkylindoles.

6.3 Experimental

Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer using TMS as the internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent peak as the reference. Elemental analyses (C, H, N) were carried out within the Department.

o-Iodoaniline was purchased neat and used without further purification (Aldrich, $67.15/25g). 1-Propargylbenzotriazole (**6.1**) was prepared from benzotriazole and propargyl bromide (80% in toluene) in ethanolic sodium hydroxide [92LA843]. The cupric salt **6.2** of 1-propargylbenzotriazole was prepared quantitatively according to the literature procedure [66JOC4071].

6.3.1 Preparation of 2-(Benzotriazol-1-ylmethyl)indole (**6.3**)

A mixture of the cupric salt **6.2** of 1-propargylbenzotriazole (3.64 g, 20 mmol) and *o*-iodoaniline (4.38, 20 mmol) in absolute DMF (100 mL) was heated at 110 °C under nitrogen for 22 h. The dark reaction mixture was filtered and the DMF distilled off under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), washed with water (3 x 100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the crude product, which was purified by recrystallization from chloroform (2.98 g, 60%) (Table 6.1): ^{1}H NMR ($CDCl_3$) δ 10.84 (s, 1 H), 7.98 (d, J = 8.1 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.41-7.29 (m, 3 H), 7.12-7.06 (m, 1 H), 7.03-6.98 (m, 1 H), 6.53 (s, 1 H), 6.01 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 145.1, 136.1, 131.9, 130.7, 126.9, 126.5, 123.1, 121.1, 119.5, 118.8, 118.6,

110.7, 109.4, 101.4, 45.1.

6.3.2 General Procedure for the Lithiation of **6.3** and Subsequent Reaction with Electrophiles

To a stirred solution of 2-(benzotriazol-1-ylmethyl)indole (**6.3**) (1 eq) in THF was added dropwise a solution of *n*-butyllithium (2.1 eq, 2.0 *M* in hexane) at -78 °C under nitrogen. The mixture was warmed to -30 °C for 30 min (or stirred at -78 °C for 5 h) and then cooled to -78 °C. The appropriate alkyl halide (1.1 eq, see Table 1) was added to the mixture and the solution was stirred for an additional 3 h at -78 °C. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was separated, washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the corresponding crude products **6.8**, which were purified either by recrystallization or column chromatography (Tables 6.1, 6.4 and 6.5).

Compounds **6.6** were obtained by quenching the dilithium salt **6.5** with three equivalents of alkyl halide together with HMPA (equal amount to THF) at -30 °C. The solution was allowed to warm to room temperature and stirred overnight. The isolation and purification procedure was as described above (Tables 6.1, 6.4 and 6.5).

Compounds **6.9** were obtained by the treatment of dilithium salt **6.5** with 1.1 equivalents of alkyl halide at -78 °C for 3 h, followed by the addition of two equivalents of a second alkyl halide together with HMPA (equal amount to THF) at -30 °C. The reaction mixture was stirred at room temperature overnight. The isolation and purification procedure was the same as described above (Tables 6.1, 6.4 and 6.5).

6.3.3 Substitution of *N*-Alkyl-2-(1-benzotriazol-1-ylalkyl)indoles **6.6** and **6.9** with Grignard Reagents

To a solution of *N*-alkyl-2-(1-benzotriazol-1-ylalkyl)indole **6.6** or **6.9** (2 mmol) in toluene was added a Grignard reagent (5 mmol in diethyl ether) under nitrogen. The mixture was refluxed for 3 h. After cooling, the solvent was distilled off under reduced pressure and the residue was dissolved in diethyl ether (50 mL), washed with water (3 x 30 mL), and dried ($MgSO_4$). The solvent was removed and the crude products purified by column chromatography to afford the pure products **6.10** (Tables 6.2, 6.6 and 6.7).

6.3.4 Preparation of 6,12-Dihydroindolo[3,2-b]carbazoles **6.11** and 5,11-Dihydro-indolo[3,2-b]carbazoles **6.13**

A solution of compound **6.6** or **6.8** or **6.9** (2 mmol) and $ZnCl_2$ (4 mmol) in CH_2Cl_2 (100 mL) was refluxed for 3 h. After cooling, hydrochloric acid (2 *N*, 100 mL) was added and the organic phase was separated, washed with aqueous sodium hydroxide (5%, 3 x 100 mL) and dried ($MgSO_4$). The solvent was removed and the residue was subjected to column chromatography on silica gel using CH_2Cl_2 / hexane (1:4) as the eluent to afford the pure products **6.11**. Alternatively, the residue was washed with a small amount of CH_2Cl_2 to give the pure compounds **6.13** (Tables 6.3, 6.8 and 6.9).

Table **6.1** Preparation of 2-(1-Benzotriazol-1-ylalkyl)indoles **6.3**, **6.6**, **6.8** and **6.9**

compd	R^1X	R^2X	yield (%)	mp (^oC)	crystal form	molecular formula	found (calcd)		
							C	H	N
6.3	-	-	60	123-124	needles[a]	$C_{15}H_{12}N_4$	72.51(72.56)	4.85 (4.87)	22.71 (22.57)
6.6a	CH_3I	-	80	143-144	powder[b]	$C_{17}H_{16}N_4$	73.76 (73.89)	5.83 (5.86)	20.26 (20.27)
6.6b	$PhCH_2Br$	-	92	170-172	needles[c]	$C_{29}H_{24}N_4$	81.24 (81.27)	5.62 (5.65)	13.04 (13.08)
6.6c	*n*-BuI	-	89	68-70	needles[c]	$C_{23}H_{28}N_4$	76.92 (76.62)	8.08 (7.83)	15.15 (15.55)
6.8a	*n*-BuI	-	98	103-104	prisms[c]	$C_{19}H_{20}N_4$	74.84 (74.97)	6.59 (6.62)	18.36 (18.41)
6.8b	*n*-$C_5H_{11}I$	-	74	99-100	powder[c]	$C_{20}H_{22}N_4$	75.22 (75.43)	6.93 (6.97)	17.68 (17.60)
6.8c	*n*-$C_6H_{13}I$	-	75	86-87	powder[c]	$C_{21}H_{24}N_4$	76.22 (75.86)	7.53 (7.28)	16.58 (16.86)
6.9a	*n*-BuI	$PhCH_2Br$	83	103-105	powder[c]	$C_{26}H_{26}N_4$	79.44 (79.14)	6.73 (6.65)	13.84 (14.21)
6.9b	*i*-PrI	CH_3I	84	132-133	needles[c]	$C_{19}H_{20}N_4$	75.30 (74.96)	6.70 (6.63)	18.30 (18.41)
6.9c	$PhCH_2Br$	*n*-BuI	76	-	oil[b]	$C_{26}H_{26}N_4$	79.48 (79.14)	6.74 (6.65)	13.99 (14.21)
6.9d	CH_3I	EtI	76	-	oil[b]	$C_{18}H_{18}N_4$	74.72 (74.44)	6.25 (6.25)	19.24 (19.30)
6.9e	EtI	CH_3I	84	-	oil[b]	$C_{18}H_{18}N_4$	74.76 (74.44)	6.46 (6.25)	19.31 (19.30)

[a] From chloroform. [b] Column chromatography ($CHCl_3$ / hexane). [c] From ethyl acetate and hexane.

Table **6.2** Preparation of 2-Substituted Indoles **6.10**

compd[a]	R^1	R^2	R^3MgX	yield (%)	mp (°C)	molecular formula	found (calcd)		
							C	H	N
6.10a	CH_3	CH_3	CH_3MgI	90	oil	$C_{12}H_{15}N$	82.95 (83.19)	8.80 (8.73)	7.93 (8.08)
6.10b	$PhCH_2$	$PhCH_2$	PhMgBr	78	115-116	$C_{29}H_{25}N$	89.71 (89.88)	6.53 (6.51)	3.60 (3.62)
6.10c	*n*-Bu	*n*-Bu	EtMgI	68	oil	$C_{19}H_{29}N$	84.15 (84.07)	11.03 (10.77)	5.10 (5.16)
6.10d	*n*-Bu	$PhCH_2$	EtMgI	62	oil	$C_{22}H_{27}N$	86.81 (86.50)	9.07 (8.92)	4.47 (4.59)
6.10e	*i*-Pr	CH_3	CH_3MgI	88	oil	$C_{14}H_{19}N$	83.80 (83.52)	9.73 (9.52)	6.83 (6.96)
6.10f	$PhCH_2$	*n*-Bu	PhMgBr	70	oil	$C_{26}H_{27}N$	88.63 (88.33)	7.89 (7.70)	3.84 (3.96)

[a] Isolated by column chromatography (CH_2Cl_2 / hexane).

Table **6.3** Preparation of Indolo[3,2-b]carbazoles **6.11** and **6.13**

compd[a]	yield (%)	mp (°C)	molecular formula	analysis / HRMS					
				found			calcd		
				C	H	N	C	H	N
6.11a	80	262-263	$C_{22}H_{22}N_2$	84.02	7.03	8.82	84.03	7.06	8.91
6.11b	61	208-210	$C_{24}H_{26}N_2$	84.51	7.72	8.07	84.16	7.66	8.18
6.11c	48	90-91	$C_{24}H_{26}N_2$	342.2096			342.2096		
6.13a	63	287-290	$C_{26}H_{28}N_2$	84.59	7.75	7.56	84.74	7.66	7.60
6.13b	57	271-273	$C_{28}H_{32}N_2$	396.2590			396.2565		
6.13c	64	257-258	$C_{30}H_{36}N_2$	84.77	8.64	6.56	84.85	8.55	6.60

[a]All compounds were isolated as powders.

Table **6.4** ^{1}H NMR Spectral Data (δ in ppm, *J* in Hz) of Compounds **6.6**, **6.6** and **6.9** ($CDCl_3$)

compd	aromatic protons	NH	Bt-CH	aliphatic protons
6.6a	7.99 (d, 8.2, 1 H), 7.66 (d, 8.4, 1 H), 7.21-7.07 (m, 6 H), 6.82 (s, 1 H)	-	6.45 (q, 7.0)	3.24 (s, 3 H), 2.06 (d, 7.0, 3 H)
6.6b	7.87-7.84 (m, 1 H), 7.74-7.71 (m, 1 H), 7.24-6.98 (m, 13 H), 6.85-6.82 (m, 2 H), 6.60 (d, 7.2, 2 H)	-	6.40 (t, 7.7)	5.19 (d, 17.3, 1 H), 5.10 (d, 17.3, 1 H), 3.85-3.78 (m, 2H).
6.6c	8.05-8.00 (m, 1 H), 7.69 (d, 7.6, 1 H), 7.44-7.39 (m, 1 H), 7.29-7.10 (m, 5 H), 6.92 (s, 1 H)	-	6.37 (dd, 7.7 and 6.9)	4.03-3.86 (m, 2 H), 2.64-2.57 (m, 2 H), 1.50-1.10 (m, 8 H), 0.88 (t, 7.2, 3 H), 0.77 (t, 7.2, 3 H)
6.8a	7.65 (d, 8.4, 1 H), 7.52 (d, 8.4, 1 H), 7.38 (d, 7.7, 1 H), 7.24 (d, 7.3, 1 H), 7.16-7.07 (m, 3 H), 7.01-6.98 (m, 1 H), 6.73 (s, 1 H)	10.36 (s)	6.20 (t, 7.6)	2.59-2.52 (m, 2 H), 1.36-1.09 (m, 4 H), 0.80 (t, 7.2, 3 H)
6.8b	7.89 (d, 8.2, 1 H), 7.62 (d, 7.7, 1 H), 7.42-7.08 (m, 6 H), 6.69 (s, 1 H)	9.02 (br s)	6.14 (t, 7.2)	2.69-2.50 (m, 2 H), 1.46-1.11 (m, 6 H), 0.83 (t, 6.9, 3 H)
6.8c	7.79 (d, 8.3, 1 H), 7.64 (d, 8.2, 1 H), 7.39-7.08 (m, 6 H), 6.71 (s, 1 H)	9.45 (s)	6.17 (t, 7.7)	2.64-2.56 (m, 2 H), 1.41-1.16 (m, 8 H), 0.84 (t, 6.8, 3 H)
6.9a	7.87-7.84 (m, 1 H), 7.72-7.69 (m, 1 H), 7.35-7.32 (m, 1 H), 7.18-6.92 (m, 9 H), 6.59 (d, 6.7, 2 H)	-	6.20 (t, 7.7)	5.24 (d, 17.3, 1 H), 5.08 (d, 17.3, 1 H), 2.58-2.45 (m, 2 H), 1.32-1.00 (m, 4 H), 0.76 (t, 7.2, 3 H)
6.9b	8.03-7.99 (m, 1 H), 7.67 (d, 7.7, 1 H), 7.52-7.49 (m, 1 H), 7.27-7.09 (m, 5 H), 6.93 (s, 1 H)	-	5.97 (d, 10.6)	3.53 (s, 3 H), 3.26-3.13 (m, 1 H), 1.28 (d, 6.6, 3 H), 0.75 (d, 6.6, 3 H)
6.9c	7.99-7.94 (m, 1 H), 7.68 (d, 7.6, 1 H), 7.44-7.38 (m, 1 H), 7.24-7.05 (m, 8 H), 7.00 (s, 1 H), 6.91-6.86 (m, 2 H)	-	6.51 (t, 7.7)	3.96-3.79 (m, 4 H), 1.41-1.29 (m, 1 H), 1.13-1.00 (m, 2 H), 0.70-0.58 (m, 1 H), 0.68 (t, 7.3, 3 H)
6.9d	8.03 (d, 8.0, 1 H), 7.71 (d, 7.7 1 H), 7.30-7.12 (m, 6 H), 6.90 (s, 1 H)	-	6.56 (q, 6.4)	4.13-3.87 (m, 2 H), 2.16 (d, 7.2, 3 H), 0.75 (t, 7.2, 3 H)
6.9e	8.03 (d, 8.2, 1 H), 7.68 (d, 7.7 1 H), 7.35-7.11 (m, 6H), 6.89 (s, 1 H)	-	6.26 (t, 7.5)	3.41 (s, 3 H), 2.65-2.59 (m, 2 H), 0.98 (t, 7.2, 3 H)

Table **6.5** ^{13}C NMR Spectral Data (δ in ppm) of Compoumds **6.6**, **6.8** and **6.9** ($CDCl_3$)[a]

compd	Bt						indole	CH	R^1 and R^2
	C-4	C-5	C-6	C-7	C-3a	C-7a			
6.6a	120.7	123.6	127.0	110.3	146.4	131.2	137.8, 135.4, 126.4, 122.2, 119.6 (2 C), 109.0, 101.5	52.5	29.2, 19.0
6.6b	120.2	123.6	127.1	110.1	146.3	131.9	137.9, 136.4, 126.9, 122.8, 121.1, 120.0, 109.8, 103.1	58.1	136.1, 134.9, 128.6, 128.5, 128.4, 127.0, 125.4, 46.4, 39.4
6.6c	121.0	123.9	127.2	110.7	146.8	131.6	137.2, 134.7, 126.9, 122.3, 120.0, 119.8, 109.7, 101.9	57.2	43.3, 32.4, 31.7, 28.4, 22.1, 20.0, 13.7, 13.6
6.8a	119.6	123.9	127.0	110.1	145.6	131.7	136.9, 135.1, 127.4, 122.2, 120.4, 118.8, 111.4, 101.1	58.4	32.7, 28.1, 21.9, 13.6
6.8b	120.6	124.1	127.3	111.3	145.9	132.1	136.8, 135.1, 127.5, 122.5, 119.9, 119.5, 110.0, 101.4	58.3	33.6, 31.1, 25.9, 22.3, 13.9
6.8c	120.6	124.1	127.4	111.3	146.0	132.1	136.8, 135.1, 127.5, 122.5, 120.0, 119.6, 110.0, 101.4	58.3	33.7, 31.4, 28.6, 26.2, 22.5 13.9
6.9a	120.8	123.5	128.1	110.4	146.4	131.5	137.8, 135.1, 126.7, 122.6, 120.0, 119.8, 109.6, 102.5	56.7	136.3, 126.8, 125.2, 46.2, 32.2, 28.1, 21.7, 13.5
6.9b	120.7	123.8	127.1	110.6	146.5	131.8	137.6, 134.3, 126.7, 122.2, 119.8, 119.7, 109.2, 102.1	63.4	30.8, 29.6, 21.2, 19.4
6.9c	120.0	123.8	127.2	110.3	146.5	131.8	137.1, 134.3, 126.9, 122.4, 121.0, 119.8, 109.7, 102.2	58.4	136.1, 128.6, 128.5, 127.0, 43.3, 39.1, 31.6, 19.9, 13.5
6.9d	121.1	123.9	127.3	110.7	146.7	131.5	137.0, 135.0, 127.0, 122.5, 120.0, 119.9, 109.6, 101.9	52.8	38.1, 19.3, 14.5
6.9e	120.9	123.9	127.2	110.7	146.8	131.5	137.9, 135.0, 126.7, 122.4, 120.0, 119.8, 109.2, 101.7	58.9	29.6, 25.9, 11.0

[a] All assignments for aromatic carbons are tentative.

Table **6.6** ^{1}H NMR Spectral Data (δ in ppm, *J* in Hz) of 2-Substituted Indoles **6.10** ($CDCl_3$)

compd	indole	CH	R^1, R^2 and R^3
6.10a	7.53 (d, 7.8, 1 H), 7.22 (d, 8.1, 1 H), 7.13 (dd, 8.1 and 7.0, 1 H), 7.05 (dd, 7.8 and 7.0, 1 H), 6.25 (s, 1 H)	3.04 (septet, 6.8)	3.62 (s, 3 H), 1.31 (d, 6.8, 6 H)
6.10b	7.66-7.63 (m, 1 H), 7.19-7.06 (m, 3 H), [a] 6.70 (s, 1 H)	4.20 (t, 7.7)	7.19-7.06 (m, 9 H),[a] 7.01-6.98 (m, 2 H), 6.90-6.87 (m, 2 H), 6.77-6.74 (m, 2 H), 5.12 (d, 17.1, 1 H), 4.90 (d, 17.1, 1 H), 3.48 (dd, 13.7 and 7.4, 1 H), 3.17 (dd, 13.7 and 7.7, 1 H)
6.10c	7.55 (d, 7.1 1 H), 7.28 (d, 8.3, 1 H), 7.15-7.03 (m, 2 H), 6.23 (s, 1 H)	2.75-2.69 (m)	4.07 (t, 7.7, 2 H), 1.77-1.66 (m, 6 H), 1.45-1.23 (m, 6 H), 0.98-0.84 (m, 9 H)
6.10d	7.59-7.55 (m, 1 H), 7.22-7.03 (m, 3 H),[a] 6.31 (s, 1 H)	2.69-2.60 (m)	7.22-7.03 (m, 3 H),[a] 6.90 (d, 7.4, 2 H), 5.29 (s, 2 H), 1.66-1.55 (m, 4 H), 1.18-1.09 (m, 4 H), 0.82-0.74 (m, 6 H)
6.10e	7.54 (d, 7.7, 1 H), 7.25 (d, 8.1, 1 H), 7.17-7.04 (m, 2 H), 6.25 (s, 1 H)	2.82-2.72 (m)	3.65 (s, 3 H), 1.96-1.85 (m, 1 H), 1.27 (d, 7.0, 3 H), 0.95 (d, 6.8, 3 H), 0.90 (d, 6.7, 3 H)
6.10f	7.50 (d, 6.9, 1 H), 7.06-6.92 (m, 3 H),[a] 6.50 (s, 1 H)	4.14 (dd, 8.8 and 6.3)	7.06-6.92 (m, 6 H),[a] 6.89-6.80 (m, 4 H), 3.62 (t, 8.3, 2 H), 3.42 (dd, 13.5 and 6.3), 3.06 (dd, 13.5 and 8.8), 1.41-1.26 (m, 1 H), 1.06-0.81 (m, 3 H), 0.62 (t, 7.3, 3 H)

[a] Signals of indole and Ph are overlapped.

Table **6.7** ^{13}C NMR Spectral Data (δ in ppm) of 2-Substituted Indoles **6.10** ($CDCl_3$)

compd	indole	CH	R^1, R^2 and R^3
6.10a	147.4, 137.2, 127.7, 120.4, 119.7, 119.0, 108.6, 96.0	26.7	28.1, 22.4
6.10b	142.4, 142.3, 127.9, 121.3, 120.2, 119.5, 109.3, 100.7	45.5	139.5, 137.8, 137.3, 129.0, 128.6, 128.4, 128.1, 127.1, 126.6, 126.0, 125.9, 46.3, 42.9
6.10c	145.1, 136.3, 128.3, 120.0, 119.7, 119.0, 109.1, 97.3	38.2	42.8, 35.5, 32.6, 29.7, 28.9, 22.9, 20.3, 14.0, 13.8, 11.8
6.10d	145.3, 137.0, 128.3, 120.6, 119.8, 119.5, 109.4, 98.3	38.1	138.2, 128.6, 127.1, 126.0, 46.4, 35.1, 29.4, 28.5, 22.8, 14.0, 11.6
6.10e	146.1, 137.1, 127.9, 120.4, 119.7, 119.2, 108.8, 97.9	33.1	37.3, 29.6, 21.3, 18.6, 16.4
6.10f	142.5, 142.0, 127.8, 120.8, 120.2, 119.2, 109.2, 99.6	46.0	139.7, 136.7, 129.1, 128.3, 128.1, 128.0, 126.5, 126.0, 43.0, 42.9, 31.6, 20.1, 13.7

Table **6.8** ^{1}H NMR Spectral Data (δ in ppm, *J* in Hz) of Indolo[3,2-b]carbazoles **6.11** and **6.13**

compd	aromatic protons	aliphatic protons
6.11a[a]	7.59 (d, 7.6, 2 H), 7.33 (d, 8.0, 2 H), 7.17-7.05 (m, 4 H)	4.40 (q, 6.4, 2 H, CH), 3.79 (s, 6 H, CH_3), 1.59 (d, 6.4, 6 H, CH_3)
6.11b[a]	7.66 (d, 7.4, 2 H), 7.37 (d, 7.5, 2 H), 7.25-7.13 (m, 4 H)	4.47-4.40 (m, 2 H, CH), 4.39-4.23 (m, 4 H, CH_2), 1.66 (d, 6.7, 6 H, CH_3), 1.43 (t, 7.2, 6 H, CH_3)
6.11c[a]	7.67 (d, 7.8, 2 H), 7.33 (d, 7.9, 2 H), 7.23-7.18 (m, 2 H) 7.16-7.10 (m, 2 H)	4.44-4.40 (m, 2 H, CH), 3.82 (s, 6 H, CH_3), 2.32-2.18 (m, 2 H, CH_2), 2.04-1.90 (m, 2 H, CH_2), 0.98 (t, 7.5, 6 H, CH_3)
6.13a[b]	10.81 (s, 2 H, NH), 8.00 (d, 7.9, 2 H), 7.40 (d, 8.0, 2 H) 7.25 (dd, 7.9 and 7.3, 2 H), 7.01 (dd, 8.0 and 7.3, 2 H)	3.35 (t, 7.1, 4 H. CH_2), 1.67-1.50 (m, 4 H, CH_2), 1.48-1.43 (m, 4 H, CH_2), 0.84 (t, 7.2, 6 H, CH_3)
6.13b[b]	10.86 (s, 2 H, NH), 8.04 (d, 8.0, 2 H), 7.45 (d, 8.0, 2 H) 7.30 (dd, 8.0 and 7.4, 2 H), 7.07 (dd, 8.0 and 7.4, 2 H)	3.39 (t, 7.7, 4 H, CH_2), 1.78-1.68 (m, 4 H, CH_2), 1.55-1.45 (m, 4 H, CH_2), 1.38-1.26 (m, 4 H, CH_2), 0.82 (t, 7.4, 6 H, CH_3)
6.13c[a]	8.18 (d, 7.8, 2 H), 7.98 (s, 2 H, NH), 7.51 (d, 8.0, 2 H), 7.46-7.40 (m, 2 H), 7.27-7.21 (m, 2 H)	3.43 (t, 8.0, 4 H, CH_2), 1.98-1.88 (m, 4 H, CH_2), 1.67-1.56 (m, 4 H, CH_2), 1.45-1.28 (m, 8 H, CH_2), 0.90 (t, 8.0, 6 H, CH_3)

[a] In $CDCl_3$. [b] In DMSO-d_6.

Table **6.9** ^{13}C NMR Spectral Data (δ in ppm) of Indolo[3,2-b]carbazoles **6.11** and **6.13**

compd	aromatic carbons	aliphatic carbons
6.11a[a]	139.1, 137.2, 125.0, 120.3, 118.4, 117.4, 111.3, 108.7	29.2 (NCH_3), 26.2 (CH), 23.1 (CH_3)
6.11b[a]	139.3, 136.6, 126.1, 120.8, 118.9, 118.1, 112.4, 109.5	38.0 (NCH_3), 27.0 (CH), 24.0, 15.4 (CH_3)
6.11c[a]	140.0, 137.8, 126.5, 120.6, 118.8, 118.6, 111.4, 109.0	33.7 (NCH_3), 30.2 (CH), 30.0 (CH_2), 12.1 (CH_3)
6.13a[b]	141.3, 134.3, 124.7, 122.8, 121.8, 119.7, 117.7, 115.3, 110.5	31.4, 28.0, 22.6 (CH_2), 14.1 (CH_3)
6.13b[b]	141.3, 134.2, 124.7, 122.8, 121.8, 119.6, 117.7, 115.3, 110.5	31.6, 28.9, 28.1, 22.3 (CH_2), 14.0 (CH_3)
6.13c[a]	140.9, 134.5, 125.2, 124.0, 122.5, 120.6, 118.8, 115.8, 110.4	32.0, 30.0, 29.3, 29.0, 22.7 (CH_2), 14.1 (CH_3)

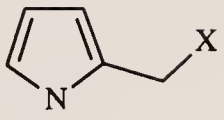
[a] In $CDCl_3$. [b] In DMSO-d_6.

CHAPTER VII
4-SUBSTITUTED AND 4,5-DISUBSTITUTED 2-(BENZOTRIAZOL-1-YL)METHYLPYRROLES AS VERSATILE SYNTHETIC INTERMEDIATES

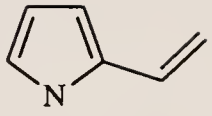
7.1 Introduction

2-(Functionalized-methyl)pyrroles **7.1** and 2-alkenylpyrroles **7.2** are important intermediates in organic synthesis, especially for natural products [84MI270 and 85JA2485]. Owing to their great synthetic importance, a wide range of pyrrole intermediates containing 2-CH_2X groups have been studied [84MI270 and 77MI355], in which X is halogen, hydroxy, alkoxy, alkylthio, amino, cyano, etc. as shown in Block 7.1. Among these, halogenomethyl groups have been most frequently employed inter alia for the preparation of other -CH_2X groups by nucleophilic substitutions. However, the use of CH_2-halogen groups is limited to pyrroles in which all the ring carbons are substituted, otherwise difficulties arise from instability and the sensitivity to intermolecular nucleophilic attack to form polymers rapidly [84MI270, 63CR511, 78LA2024, 80JA1377 and 80JOC1786]. Quaternary ammonium groups of type -$CH_2N^+R_3$ can also be displaced by nucleophiles [77MI355]. Other functional groups X mentioned are less susceptible to nucleophilic substitution. In most cases, the base-assisted alkylation can not be achieved, except for 2-cyanomethyl- and 2-alkoxycarbonylmethyl-pyrroles [84MI270]. Furthermore, the alkylation and subsequent nucleophilic substitution of CH_2X to give CHRNu or the elimination to form 2-alkenylpyrroles **7.2**, another class of important compounds, have not been

previously reported.



7.1



7.2

X = halogen, OH, OR, SR, NH_2, NR_2, $^+NR_3$, CN, carboxylate, $^+PPh_3$, N_3

Block 7.1

We now report a convenient method for the synthesis of 4-mono- and 4,5-di-substituted-2-(benzotriazol-1-yl)methylpyrroles **7.7** and **7.15** and the elaborations of their side chain 2-(benzotriazol-1-yl)methyl group by nucleophilic substitution or first alkylation followed by replacement or elimination of the benzotriazolyl group which allows the preparation of elaborated pyrroles unsubstituted at the 3- and 5-positions and at the 3-positions.

7.2 Results and Discussion

7.2.1 Preparation of 4-mono- and 4, 5-di-substituted-2-(benzotriazol-1-yl)-methylpyrroles **7.7** and **7.15**

In chapter V, we described the synthesis of substituted furans by base-catalyzed cyclization of alkynyloxiranes **7.4** and **7.14** which were easily prepared from the reaction of 1-propargylbenzotriazole (**7.3**) with α-bromoketones [95JOC638]. The epoxides of types **7.4** and **7.14** now have been further utilized for the preparation of pyrrole systems: **7.4** and **7.14** refluxing with primary amines in

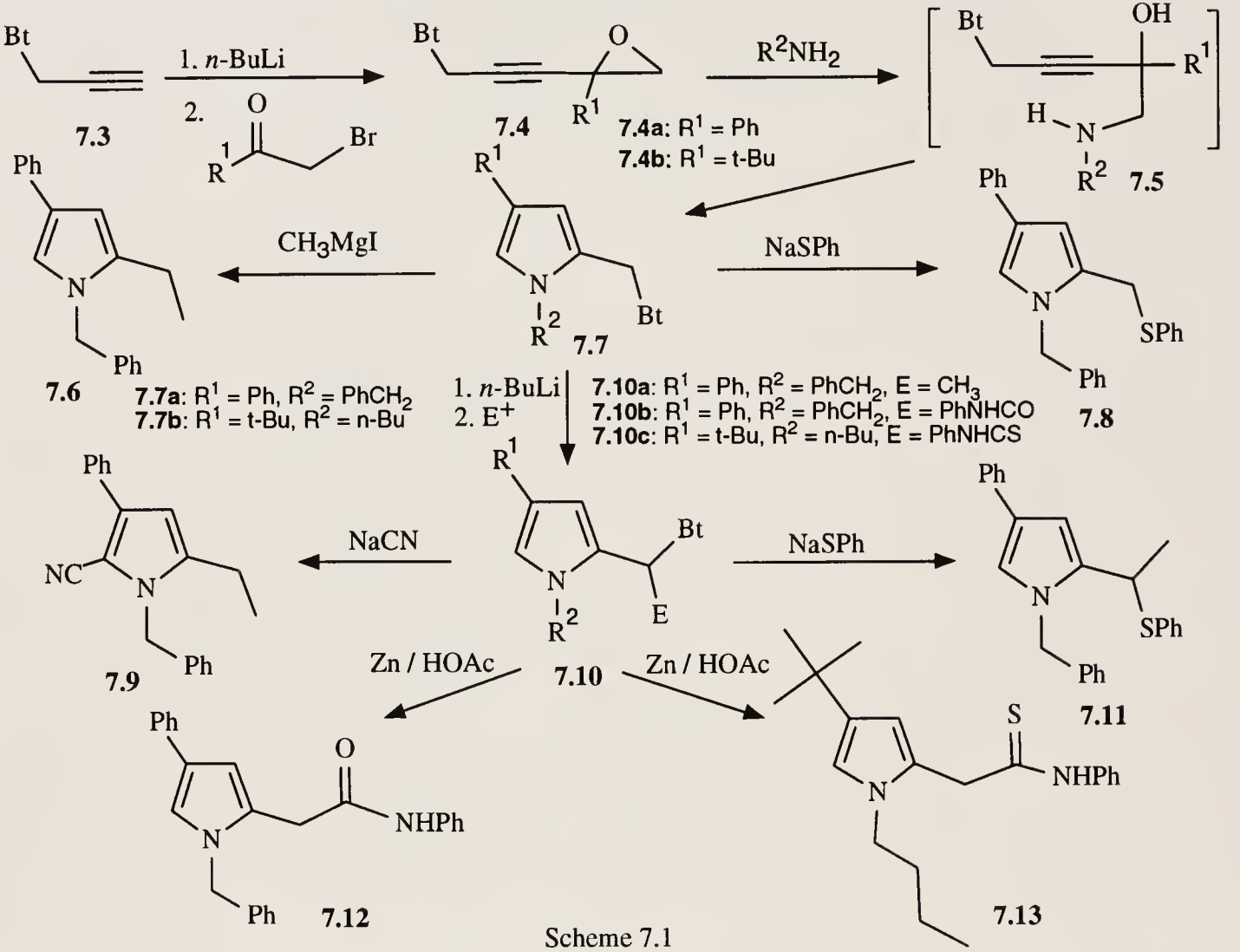
i-PrOH gave 4-mono- (**7.7**, Scheme 7.1) and 4, 5-di-substituted-2-(benzotriazol-1-yl)-methylpyrroles (**7.15**, Scheme 7.3) in good yields. A similar reaction was previously reported for other alkynyloxiranes without using solvents [58ZOK2360]. However, our alkynyloxiranes **7.4** or **7.14** with amines under these reaction conditions gave furans as major products [95JOC638], presumably 1,4-elimination of **7.4** and **7.14** was predominated instead of nucleophilic attack at epoxide ring under these reaction conditions. Therefore, in the present cases, solvent is essential and the yields were better with *i*-PrOH than with DMF.

7.2.2 Elaboration of the 2-(Benzotriazol-1-yl)methyl Side Chain

Work in our laboratory has demonstrated that benzotriazole is a good synthetic auxiliary [95UP2]. The good leaving ability and the anion-stabilizing capability are two of its advantageous features which have been well recognized. Thus, compounds **7.7a** readily underwent nucleophilic substitution with methylmagnesium iodide and sodium thiophenolate to give the corresponding products **7.6** and **7.8** respectively in good yields (Scheme 7.1). The electron-rich pyrrole nucleus assisted the reaction by stabilizing the transient carbocations.

It is well-known that pyrroles smoothly undergo 2-lithiation, however, in the case of compounds **7.7**, lithiation occurred regiospecifically at the carbon attached to benzotriazolyl group due to the electron withdrawing ability of the benzotriazolyl moiety. Accordingly, the 3,5-unsubstituted-2-(benzotriazol-1-yl)methylpyrroles **7.7a-b** were easily alkylated by lithiation and subsequent quenches with electrophiles including methyl iodide, phenyl isocyanate and phenyl isothiocyanate to give the corresponding product **7.10a-c** in high yields. The nucleophilic substitution of

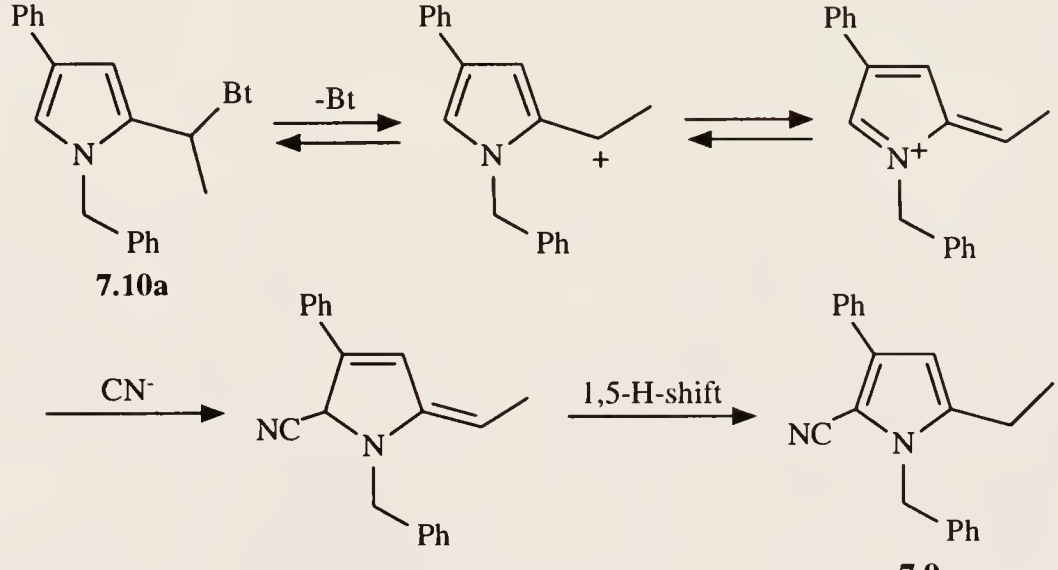
Preparation and Subsequent Elaboration of 4-Substituted 2-(Benzotriazol-1-yl)methylpyrroles



Scheme 7.1

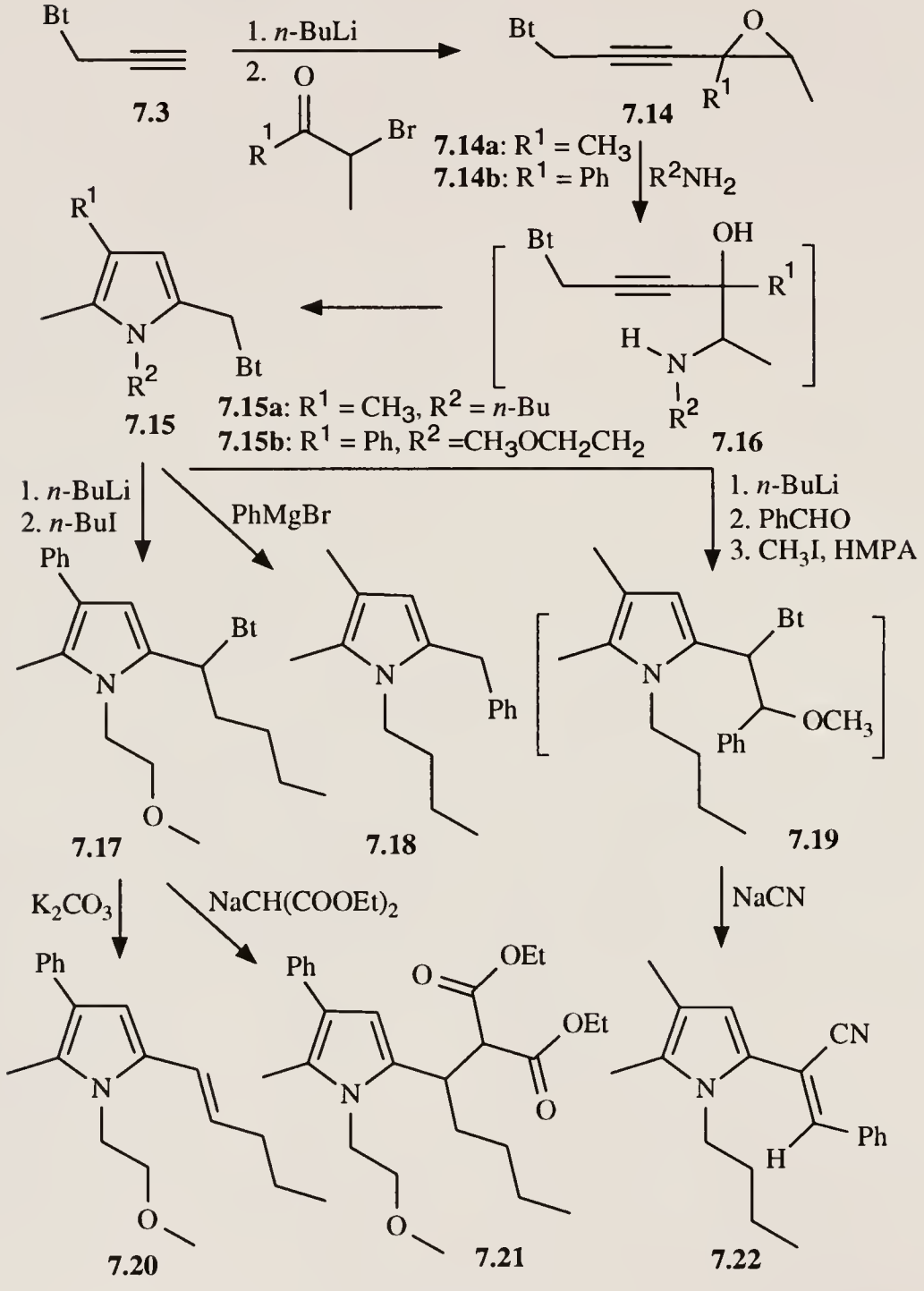
benzotriazolyl group in the substituted intermediates **7.10a** with sodium thiophenolate was much faster than that of compounds **7.7a** due to the stabilization of intermediate carbocation by the directly attached methyl group and the reaction gave the product **7.11** in higher yield (Table 7.1). Compounds of type **7.10b** and **7.10c** readily underwent reductive elimination of benzotriazole when they were treated with zinc in the presence of acidic acid to generate pyrrol-2-yl-acetanilide **7.12** and -thioacetanilide **7.13** respectively.

Interestingly, the reaction of **7.10a** with sodium cyanide in DMF gave S_N' type of "abnormal" product **7.21** in 52% yield, this result strongly supported the S_N1 pathway as described by Maryanoff and her coworkers [77JOC1096]. The proposed mechanism is illustrated in scheme 7.2. We were unable to isolate other possible isomers by column chromatography.



Scheme 7.2

Preparation and Subsequent Elaboration of 4,5-Disubstituted 2-(Benzotriazol-1-yl)methylpyrroles



Scheme 7.3

Similarly, the benzotriazolyl group of the 3-unsubstituted 2-(benzotriazol-1-yl)methylpyrroles **15a** was readily replaced by phenylmagnesium bromide to give compound **7.18** (Scheme 7.3). Compound **7.15b** was treated with 1.1 equiv of *n*-BuLi at -78 °C for 1 h and followed by reaction with *n*-butyl iodide to yield product **7.17.** Upon treatment with potassium carbonate in DMF under reflux, compound **7.17** underwent base-catalyzed elimination of benzotriazole to form alkenylpyrrole **7.20** which is stable and can be isolated by column chromatography. When the compound **7.17** was refluxed with sodium malonate in DMF for 12 h, the substituted product of type **7.21** was obtained in 76% yield. Treatment of compound **7.15** with 1.1 equiv of *n*-butyllithium followed quench with benzaldehyde to generate the alkylated anion which was trapped by addition of methyl iodide and HMPA to give the intermediate **7.19**. **7.19** was treated with sodium cyanide without purification to undergo first nucleophilic substitution of benzotriazolyl group with cyanide and then elimination of methanol to afford vinylpyrrole **7.22.**

All products are novel and were characterized by ^{1}H and ^{13}C NMR spectra and elemental analyses (see experimental and Table 7.1)

In conclusion, 4-mono- and 4,5-di-substituted-2-(benzotriazol-1-yl)-methylpyrroles **7.7** and **7.15**, derived from the reaction of alkynyloxiranes **7.4** and **7.14** with α-bromoketones, readily underwent nucleophilic replacements of their benzotriazolyl group with Grignard reagents and sodium thiophenolate. Compounds **7.7** and **7.15** were alkylated *via* lithiation and subsequent quenches with electrophiles to give intermediates **7.10**, **7.17** and **7.19** in which benzotriazolyl group could either be replaced by a variety of nucleophiles or eliminated in the presence of a base. Compounds **7.10b-c** were reduced by zinc in acetic acid to afford the corresponding products **7.12** and **7.13**. The above benzotriazole mediated transformations should

find the general use in synthesis including natural products.

7.3 Experimental

Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent peak ($CDCl_3$) as the reference. Elemental analyses (C. H. N) were carried out within the department.

1-Propargylbenzotriazole (**7.3**) was prepared according to the procedure described in chapter II. All α-bromoketones were purchased neat and used without further purification. The preparation of compound **7.14a** was reported in chapter V [95JOC638].

7.3.1 Preparation of Epoxides **7.4a,b** and **7.14b**

To a stirred solution of 1-propargylbenzotriazole (**7.3**) (1.57 g, 10 mmol) in THF (50 mL) was added at -78 °C a solution of *n*-BuLi (5.5 mL, 11 mmol, 2.0 *M* in cyclohexane). The mixture was stirred at this temperature for 1 h and α-bromoketone (indicated in schemes 7.1 and 7.3) (10 mmol) in THF (5 mL) was added slowly. After stirring at -78 °C for 5 to 8 h, diethyl ether (100 mL) and water (100 mL) were added and the organic phase was separated, washed with saturated NH_4Cl solution (100 mL x 3) and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by column chromatography using EtOAc/hexane (1:4) as the eluent to afford the pure product.

5-(Benzotriazol-1-yl)-1,2-epoxy-2-phenyl-3-pentyne (**7.4a**): oil, yield 76%: ^{1}H NMR δ 8.05 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H), 7.46-7.52 (m, 1 H), 7.28-7.41 (m, 6 H), 5.55 (s, 2 H), 3.35 (d, *J* = 6.0 Hz, 1 H), 2.97 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR δ 145.9, 135.9, 132.2, 128.3, 128.2, 127.5, 125.1, 124.0, 119.8, 109.5, 84.1, 75.9, 58.6, 50.5, 38.0. Anal. calcd for $C_{17}H_{13}N_3O$: C, 74.15; H, 4.76; N, 15.27. Found: C, 74.03; H, 4.77; N, 15.37.

5-(Benzotriazol-1-yl)-1,2-epoxy-2-(*t*-butyl)-3-pentyne **7.4b**: solid, yield 76%: mp 49-50 °C; ^{1}H NMR δ 8.09 (d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.51-7.57 (m, 1 H), 7.30-7.44 (m, 1 H), 5.51 (s, 2 H), 2.93 (d, *J* = 5.2 Hz, 1 H), 2.86 (d, *J* = 5.2 Hz, 1 H), 0.97 (s, 9 H); ^{13}C NMR δ 146.2, 132.4, 127.6, 124.1, 120.1, 109.6, 85.4, 74.5, 57.1, 51.5, 38.2, 33.2, 25.4. Anal. calcd for $C_{15}H_{17}N_3O$: C, 70.55; H, 6.72: N, 16.47. Found: C, 70.22; H, 6.69; N, 16.77.

5-(Benzotriazol-1-yl)-1,2-epoxy-1-methyl-2-phenyl-3-pentyne (**7.14b**): oil, yield 67%: ^{1}H NMR δ 8.05 (d, *J* = 8.3 Hz, 1 H), 7.66 (d, *J* = 8.3 Hz, 1 H), 7.46-7.51 (m, 1 H), 7.30-7.42 (m, 6 H), 5.51 (s, 2 H), 3.53 (q, *J* = 5.4 Hz, 1 H), 1.01 (d, *J* = 5.4 Hz, 3 H); ^{13}C NMR δ 146.0, 134.3, 132.3, 128.1, 128.0, 127.5, 126.7, 124.0, 119.9, 109.6, 86.2, 74.5, 62.7, 55.2, 38.1, 12.9. Anal. calcd for $C_{18}H_{15}N_3O$: C, 74.71; H, 5.23; N, 14.53. Found: C, 74.37; H, 5.24; N, 14.73.

7.3.2 Preparation of 4-Mono- and 4,5-Di-substituted-2-(benzotriazol-1-yl)methyl-pyrroles **7.7** and **7.15**

A solution of epoxide **7.4** or **7.14** and appropriate primary amine (see schemes 7.1 and 7.3) in *i*-PrOH was refluxed for 24 to 48 h. After cooling, the solvent was distilled off under reduced pressure to give an oil which was purified by short column chromatography using EtOAc/hexane as the eluent to afford the corresponding

product.

N-Benzyl-2-(benzotriazol-1-yl)methyl-4-phenylpyrrole (**7.7a**): needles, yield 82%: mp 157-158 °C: ^{1}H NMR δ 7.97 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 7.2 Hz, 2 H), 7.16-7.44 (m, 9 H), 7.02 (d, *J* = 1.9 Hz, 1 H), 6.90-6.92 (m, 2 H), 6.76 (d, *J* = 1.9 Hz, 1 H), 5.74 (s, 2 H), 5.08 (s, 2 H); ^{13}C NMR δ 146.3, 136.8, 135.0, 132.7, 128.7, 128.6, 127.6, 127.3, 126.3, 125.8, 125.6, 124.9, 124.0, 123.9, 120.9, 119.9, 110.1, 109.8, 50.9, 44.9. Anal. calcd for $C_{24}H_{20}N_4$: C, 79.08; H, 5.53; N, 15.38. Found: C, 78.81; H, 5.46; N, 15.35.

N-(*n*-Butyl)-2-(benzotriazol-1-yl)methyl-4-(*t*-butyl)pyrrole (**7.7b**): solid, yield 63%: mp 69-70 °C; ^{1}H NMR δ 8.01 (d, *J* = 8.2 Hz, 1 H), 7.26-7.37 (m, 3 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 6.31 (d, *J* = 2.0 Hz, 1 H), 5.79 (s, 2 H), 3.73 (t, *J* = 7.4 Hz, 2 H), 1.02-1.40 (m, 4 H), 1.25 (s, 9 H), 0.79 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR δ 146.2, 134.5, 132.7, 127.0, 123.6, 123.2, 119.6, 117.7, 110.2, 108.8, 46.3, 45.1, 33.2, 31.6, 30.3, 19.7, 13.5. Anal. calcd for $C_{19}H_{26}N_4$: C, 73.50; H, 8.45; N, 18.06. Found: C, 73.86; H, 8.57; N, 18.16.

N-(*n*-Butyl) -2-(benzotriazol-1-yl)methyl-4,5-dimethylpyrrole (**15a**): solid, yield 62%: mp 86-87 °C; ^{1}H NMR δ 7.99 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.24-7.37 (m, 2 H), 6.17 (s, 1 H), 5.76 (s, 2 H), 3.74 (t, *J* = 7.8 Hz, 2 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.10-1.28 (m, 4 H), 0.81 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR δ 146.1, 132.5, 126.9, 126.6, 123.5, 121.3, 119.4, 113.8, 111.5, 110.3, 45.1, 43.7, 32.9, 19.7, 13.5, 10.9, 10.5. Anal. calcd for $C_{17}H_{22}N_4$: C, 72.29; H, 7.86; N, 19.85. Found: C, 72.60; H, 7.88: N, 19.92.

N-(2-Methoxy)ethyl-2-(benzotriazol-1-yl)methyl-4-phenyl-5- methylpyrrole (**7.15b**): oil, yield 57%: ^{1}H NMR δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 1 H), 7.26-7.38 (m, 6 H), 7.17-7.21 (m, 1 H), 6.46 (s, 1 H), 5.91 (s, 2 H), 4.09 (t, *J* = 5.4 Hz,

2 H), 3.33 (t, J = 5.4 Hz, 2 H), 3.21 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR δ 146.2, 136.7, 132.7, 128.2, 127.9, 127.1, 127.0, 125.2, 123.9, 123.7, 121.4, 119.6, 110.5, 110.2, 71.8, 58.9, 45.0, 43.8, 10.9. Anal. calcd for $C_{21}H_{22}N_4O$: C, 72.79; H, 6.40; N, 16.18. Found: C, 73.12; H, 6.57; N, 16.11.

7.3.3 Alkylation of 4-Mono- and 4,5-Di-substituted-2-(benzotriazol-1-yl)methyl-pyrroles **7.7** and **7.15**

To a solution of compound **7.7** or **7.15** (5 mmol) in THF (80 mL) at -78 °C was added a solution of *n*-BuLi (5.5 mmol, 2.75 mL, 2.0 *M* in cyclohexane). The reaction mixture was stirred at -78 °C for 1 h and then a solution of an appropriate electrophile (5 mmol) in THF (5 mL) such as methyl iodide, phenyl isocyanate, phenyl isothiocyanate and butyl iodide was added. After the reaction solution was stirred for another hour, water (100 mL) was poured into the solution and the mixture was extracted with ethyl acetate (100 mL), washed with water (100 mL x 3) and dried ($MgSO_4$). The solvent was distilled off under reduced pressure to give the crude product which was purified either by recrystallization or column chromatography to afford the corresponding product in pure state.

N-Benzyl-2-(1-benzotriazol-1-yl)ethyl-4-phenylpyrrole (**7.10a**): recrystallized from EtOAc/hexane (1:3), cubes, yield 98%: mp 142-143 °C; ^{1}H NMR δ 7.91-7.95 (m, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.35-7.40 (m, 2 H), 7.18-7.27 (m, 4 H), 7.08-7.13 (m, 3 H), 7.02 (d, J = 1.6 Hz, 1 H), 6.93 (d, J = 1.6 Hz, 1 H), 6.76-6.80 (m, 2 H), 6.24 (q, J = 7.1 Hz, 1 H), 4.83 (d, J = 16.2 Hz, 1 H), 4.69 (d, J = 16.2 Hz, 1 H), 2.01 (d, J = 7.1 Hz, 3 H); ^{13}C NMR δ 148.2, 138.1, 136.7, 133.1, 131.4, 130.4, 130.1, 129.1, 128.8, 127.8, 127.4, 126.5, 125.4, 125.3, 122.5, 121.5, 112.4, 109.1, 54.1, 52.3. Anal. calcd for $C_{25}H_{22}N_4$: C, 79.34; H, 5.86; N, 14.80. Found: C, 79.34; H, 5.94; N, 14.43.

α-(*N*-Benzyl-4-phenyl)pyrrol-2-yl-α-(benzotriazol-1-yl)acetanilide (**7.10b**): recrystallized from EtOAc/hexane (1:3), powder, yield 87%: mp 104-105 °C; ^{1}H NMR δ 9.70 (s, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.34-7.44 (m, 5 H), 6.92-7.24 (m, 10 H), 6.58-6.74 (m, 4 H), 6.33 (d, *J* = 7.2 Hz, 2 H), 4.68 (d, *J* = 16.2 Hz, 1 H), 4.54 (d, *J* = 16.2 Hz, 1 H); ^{13}C NMR δ 164.5, 145.8, 137.4, 135.8, 134.5, 133.2, 128.9, 128.1, 127.8, 127.1, 125.9, 125.7, 124.7, 124.2, 121.5, 119.9, 119.0, 112.2, 109.9, 60.6, 50.4. Anal. calcd for $C_{31}H_{25}N_5O$: C, 77.00; H, 5.21; N, 14.49. Found: C, 77.29; H, 5.24; N, 14.43.

α-[*N*-(*n*-Butyl)-4-(*t*-butyl)]pyrrol-2-yl-α-(benzotriazol-1-yl)thioacetanilide (**7.10c**): recrystallized from Et_2O, powder, yield 94%: mp 147-148 °C; ^{1}H NMR δ 10.00 (s, 1 H), 8.01 (d, *J* = 8.3 Hz, 1 H), 7.72 (d, *J* = 7.7 Hz, 2 H), 7.33-7.48 (m, 5 H), 7.22-7.27 (m, 2 H), 6.54 (d, *J* = 2.0 Hz, 1 H), 6.48 (d, *J* = 2.0 Hz, 1 H), 3.59-3.73 (m, 2 H), 1.42-1.54 (m, 1 H), 1.03-1.36 (m, 12 H), 0.72 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR δ 192.8, 145.7, 138.2, 135.3, 133.4, 128.9, 128.0, 127.0, 124.3, 123.4, 122.9, 119.9, 119.0, 110.5, 108.5, 68.4, 46.8, 33.1, 31.7, 30.5, 19.8, 13.5. Anal. calcd for $C_{26}H_{31}N_5S$: C, 70.08; H, 7.01; N, 15.72. Found: C, 70.21; H, 7.08; N, 15.83.

N-(2-Methoxy)ethyl-2-(α-benzotriazol-1-yl)pentyl-4-phenyl-5-methylpyrrole (**7.17**): purified by column chromatography using EtOAc/hexane (1:4), oil, yield 77%: ^{1}H NMR δ 8.00-8.04 (m, 1 H), 7.50-7.55 (m, 1 H), 7.19-7.44 (m, 7 H), 6.67 (s, 1 H), 6.41 (t, *J* = 7.6 Hz, 1 H), 3.94-4.04 (m, 1 H), 3.80-3.89 (m, 1 H), 3.15-3.20(m, 2 H), 3.17 (s, 3 H), 2.45-2.53 (m, 2 H), 2.26 (s, 3 H), 1.26-1.47 (m, 3 H), 1.08-1.18 (m, 1 H), 0.86 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR δ 146.7, 136.9, 131.6, 128.2, 128.0, 127.4, 126.9, 126.7, 125.3, 123.7, 121.4, 119.8, 111.1, 108.4, 71.7, 58.9, 56.9, 43.5, 32.6, 28.4, 22.0, 13.7, 11.0. Anal. calcd for $C_{25}H_{30}N_4O$: C, 74.58; H, 7.52; N, 13.93. Found: C, 74.93; H, 7.55; N, 13.67.

7.3.4 Nucleophilic substitution of **7.7a** and **7.15a** with Grignard reagents

To a solution of compound **7.7a** or **7.15a** (2 mmol) in toluene (30 mL) was added a freshly prepared solution of CH_3MgI (5 mmol) in Et_2O (5 mL) at room temperature and the solution was then refluxed for the time indicated in Table 7.1. After cooling, the solvent was removed under reduced pressure and the residue was extracted with Et_2O (50 mL), washed with water (50 mL x 3) and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by column chromatography using CH_2Cl_2/hexane (1:4) as the eluent to afford the product **7.6** or **7.18**.

N-Benzyl-2-ethyl-4-phenylpyrroles **7.6**: see Table 7.1. ^{1}H NMR δ 7.47-7.50 (m, 2 H), 7.19-7.29 (m, 5 H), 7.06-7.11 (m, 1 H), 6.98 (d, J = 7.0 Hz, 2 H), 6.87 (d, J = 2.0 Hz, 1 H), 6.28 (d, J = 2.0 Hz, 1 H), 4.93 (s, 2 H), 2.43 (q, J = 7.5 Hz, 2 H), 1.19 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 138.1, 136.1, 136.0, 128.6, 128.5, 127.3, 126.3, 125.0, 124.7, 123.5, 117.5, 103.4, 50.2, 19.3, 12.8.

N-(*n*-Butyl)-2-benzyl-4,5-dimethylpyrrole **7.18**: see Table 7.1. ^{1}H NMR δ 7.11-7.28 (m, 5 H), 5.61 (s, 1 H), 3.87 (s, 2 H), 3.59 (t, J = 7.9 Hz, 2 H), 2.09 (s, 3 H), 1.98 (s, 3 H), 1.34-1.44 (m, 2 H), 1.21-1.30 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 140.0, 128.9, 128.6, 128.3, 126.0, 123.9, 113.2, 108.3, 43.7, 33.2, 33.1, 20.1, 13.7, 11.2, 9.7.

7.3.5 Nucleophilic Substitution of **7.7a** and **7.10a** with Sodium thiophenolate

A solution of compound **7.7a** or **7.10a** (1 mmol) and sodium thiophenolate (0.66 g, 5 mmol) in DMF (50 mL) under nitrogen was heated at 150 °C for the time

indicated in Table 7.1. After cooling, water (100 mL) and Et_2O (100 mL) were added. The organic phase was separated and washed with saturated NaCl solution (100 mL x 3) and dried ($MgSO_4$). After removal of the solvent, the residue was subjected to column chromatography using CH_2Cl_2/hexane (1:4) as the eluent to afford the product **7.8** or **7.11**.

N-Benzyl-2-(phenylthiomethyl)-4-phenylpyrrole **7.8**: see Table 7.1. ^{1}H NMR δ 7.50 (d, *J* = 7.2 Hz, 2 H), 7.06-7.34 (m, 13 H), 6.95 (d, *J* = 1.7 Hz, 1 H), 6.36 (d, *J* = 1.7 Hz, 1 H), 5.17 (s, 2 H), 4.00 (s, 2 H); ^{13}C NMR δ 137.7, 135.8, 135.5, 130.6, 128.8, 128.7, 128.5, 128.3, 127.6, 126.7, 126.6, 125.3, 124.8, 123.7, 119.5, 108.0, 50.7, 31.1.

N-Benzyl-2-(1-phenylthio)ethyl-4-phenylpyrrole **7.11**: see Table 7.1. ^{1}H NMR δ 7.38 (d, *J* = 7.1 Hz, 2 H), 7.10-7.26 (m, 10 H), 6.97-7.07 (m, 3 H), 6.86 (d, *J* = 1.7 Hz, 1 H), 6.31 (d, *J* = 1.7 Hz, 1 H), 5.27 (d, *J* = 16.2 Hz, 1 H), 5.03 (d, *J* = 16.2 Hz, 1 H), 4.06 (q, *J* = 6.9 Hz, 1 H), 1.49 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR δ 138.0, 135.6, 133.8, 133.5, 133.4, 128.8, 128.7, 128.5, 127.6, 127.5, 126.5, 125.2, 124.7, 123.5, 119.1, 105.8, 50.5, 39.5, 20.7.

7.3.6 Formation of *N*-Benzyl-2-cyano-3-phenyl-5-ethylpyrrole (**7.9**)

A solution of compound **7.10a** (0.76 g, 2 mmol) and NaCN (0.49, 10 mmol) in DMF (25 mL) was refluxed for 12 h. After cooling, water (100 mL) and diethyl ether (100 mL) were added and the organic phase was separated, washed with saturated NaCl solution (100 mL x 3) and dried ($MgSO_4$). The solvent was removed to give an oil which was separated by column chromatography using CH_2Cl_2/hexane (1:4) as the eluent to afford the product **7.9**: see Table 7.1. ^{1}H NMR δ 7.73 (d, *J* = 8.0 Hz, 2 H),

7.24-7.44 (m, 6 H), 7.07 (d, J = 7.2 Hz, 2 H), 6.31 (s, 1 H), 5.23 (s, 2 H), 2.51 (q, J = 7.4 Hz, 2 H), 1.23 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 142.0, 136.2, 134.6, 132.9, 128.9, 128.8, 127.8, 127.5, 126.5, 126.2, 115.2, 106.3, 100.4, 49.0, 19.8, 12.3.

7.3.7 Formation of Pyrrol-2-yl-acetanilide **7.12** and -thioacetanilide **7.13** *via* Reductive Elimination of Benzotriazole

A mixture of compound **7.10b** or **7.10c** (2 mmol), acetic acid (10 mL), THF (20 mL) and Zinc metal (2.60 g, 40 mmol) was refluxed for 12 h. After cooling, the reaction solution was filtrated and extracted with diethyl ether (100 mL). The organic phase was separated, washed with water (50 mL x 3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product which was purified either by recrystallization or by column chromatography to afford the corresponding product **7.12** or **7.13**.

α-(*N*-Benzyl-4-phenyl)pyrrol-2-ylacetanilide (**7.12**): recrystallized form EtOAc/hexane (1:4), see Table 7.1. ^{1}H NMR δ 7.53 (d, J = 7.2 Hz, 2 H), 7.17-7.38 (m, 11 H), 7.05-7.10 (m, 4 H), 6.54 (d, J = 1.9 Hz, 1 H), 5.07 (s, 2 H), 3.63 (s, 2 H); ^{13}C NMR δ 167.7, 137.3, 136.9, 135.1, 128.9, 128.8, 128.7, 128.6, 127.8, 126.6, 125.7, 124.8, 124.5, 124.4, 120.0, 119.8, 108.2, 51.0, 36.0.

α-[*N*-(*n*-Butyl)-4-(*t*-butyl)]pyrrol-2-ylthioacetanilide (**7.13**): purified by column chromatography using EtOAc/hexane (1:4) as the eluent, see Table 7.1. ^{1}H NMR δ 8.94 (s, 1 H), 7.62-7.65 (m, 2 H), 7.35-7.40 (m, 2 H), 7.23-7.26 (m, 1 H), 6.52 (d, J = 2.1 Hz, 1 H), 6.12 (d, J = 2.1 Hz, 1 H), 4.20 (s, 2 H), 3.75 (t, J = 7.4 Hz, 2 H), 1.60-1.70 (m, 2 H), 1.18-1.34 (m, 11 H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 199.1, 138.4, 135.1, 128.8, 126.6, 124.2, 122.6, 118.0, 108.1, 46.6, 46.5, 33.4, 31.8, 31.7, 30.5, 19.9, 13.6.

7.3.8 Formation of *N*-(2-Methyoxy)ethyl-2-(*tran*-1-pentenyl)-4-phenyl-5-methyl-pyrrole (**7.20**)

A solution of compound **7.17** (0.80 g, 2 mmol) and K_2CO_3 (0.84, 4 mmol) in DMF (30 mL) was heated at 120 °C for 12 h. After cooling, diethyl ether (100 mL) and water (100 mL) were added and the organic layer was separated, washed with water (100 mL x 3) and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography using EtOAc/hexane (1:4) as the eluent to give the procuct **7.20**: see Tabel 7.1. ^{1}H NMR δ 7.31-7.39 (m, 4 H), 7.16-7.22 (m, 1 H), 6.37 (s, 1 H), 6.28 (d, *J* = 16.1 Hz, 1 H), 5.99-6.06 (m, 1 H), 4.05 (t, *J* = 6.5 Hz, 2 H), 3.57 (t, *J* = 6.5 Hz, 2 H), 3.33 (s, 3 H), 2.34 (s, 3 H), 2.13-2.20 (m, 2 H), 1.44-1.54 (m, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR δ 137.4, 131.0, 129.4, 128.2, 128.1, 125.4, 125.2, 125.1, 118.8, 104.8, 72.0, 59.1, 43.3, 35.3, 22.7, 13.7, 11.1.

7.3.9 Nucleophilic Substitution of **7.17** with Sodium Malonate

To a solution of diethyl malonate (0.34 g, 2 mmol) in DMF (30 mL) was added sodium hydride (0.08 g, 2 mmol, 60% dispersion in mineral oil) at room temperature. After the mixture was stirred for 30 mins, compound **7.17** (0.40 g, 1 mmol) in DMF (5 mL) was added and the reaction solution was heated at 120 °C for 12 h. After cooling, diethyl ether (50 mL) and water (50 mL) were added and the organic phase was separated, washed with water (50 mL x 3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an oil which was separated by column chromatography using CH_2Cl_2/hexane (1:4) as the eluent to afford the product **7.21**: see Table 7.1. ^{1}H NMR δ 7.33-7.34 (m, 4 H), 7.15-7.19 (m, 1 H), 6.02 (s, 1 H), 4.16-4.27 (m, 3 H), 3.94-4.04 (m, 3 H), 3.52-3.67 (m, 4 H), 3.35 (s, 3 H), 2.34 (s, 3

H), 1.63-1.66 (m, 2 H), 1.22-1.31 (m, 7 H), 1.03 (t, J = 7.1 Hz, 3 H), 0.82-0.87 (m, 3 H); ^{13}C NMR δ168.6, 168.3, 137.7, 131.8, 128.2, 127.9, 124.8, 124.2, 121.2, 105.6, 72.0, 61.4, 61.2, 59.0, 58.4, 43.0, 36.2, 34.5, 28.9, 22.8, 14.1, 13.9, 13.8, 11.3.

7.3.10 Formation of *N*-(*n*-Butyl)-2-(1-cyano-2-phenyl)vinyl-4,5-dimethylpyrrole (**7.22**)

To a solution of compound **7.15** (1.41 g, 5 mmol) in THF (80 mL) was added a solution of *n*-BuLi (2.75 mL, 5.5 mmol, 2.0 *M* in cyclohexane) at -78 °C and was stirred for 1 h. Benzaldehyde (0.53 g, 5 mmol) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for another hour. Methyl iodide (2.84 g, 20 mmol) in HMPA (10 mL) was added and the mixture was allowed to warm to room temperature overnight. Water (100 mL) and diethyl ether (100 mL) were poured into the reaction mixture and the organic layer was separated, washed with water (100 mL x 3) and dried ($MgSO_4$). The solvent was distilled off under reduced pressure to give an oil **7.19** which was not further purified.

The above oil was dissolved in DMF (50 mL) and to which NaCN (0.98 g, 20 mmol) was added. The mixture was refluxed for 12 h. Water (100 mL) and diethyl ether (100 mL) were poured into the solution, and the organic layer was separated, washed with NaOH (2 *N*, 50 mL x 2) and water (100 mL x 3), and dried ($MgSO_4$). After removal of the solvent, the residue was subjected to column chromatography using EtOAc/hexane as the eluent to afford the product **7.22**: see Table 7.1. ^{1}H NMR δ 7.52-7.56 (m, 2 H), 7.22-7.40 (m, 5 H), 3.89 (t, J = 7.5 Hz, 2 H), 2.18 (s, 3 H), 2.05 (s, 3 H), 1.56-1.64 (m, 2 H), 1.32-1.39 (m, 2 H), 0.95 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 135.6, 131.9, 128.8, 128.2, 127.3, 125.8, 124.8, 119.7, 118.4, 114.7, 100.1, 43.2, 33.6, 19.0, 13.7, 11.2, 10.3.

Table **7.1** Reactions of 4-Mono- and 4,5-Di-substituted-2-(benzotriazol-1-yl)alkylpyrroles **7.7**, **7.10**, **7.15**, **7.17** and **7.19**

entry	substrat	reagent	solvent	temp. (^{o}C)	time (h)	product	yield (%)	mp (^{o}C)	molecular formula	found (calcd) (%)		
										C	H	N
1	**7.7a**	CH_3MgI	toluene	reflux	6	**7.6**	87	oil	$C_{19}H_{19}N$	87.13(87.31)	7.38(7.33)	5.40(5.36)
2	**7.7a**	NaSPh	DMF	150	24	**7.8**	65	99-100	$C_{24}H_{21}NS$	80.87(81.09)	5.96(5.96)	3.89(3.94)
3	**7.10a**	NaCN	DMF	reflux	12	**7.9**	52	65-66	$C_{20}H_{18}N_2$	84.22(83.87)	6.57(6.34)	9.48(9.79)
4	**7.10a**	NaSPh	DMF	150	10	**7.11**	79	96-97	$C_{25}H_{23}NS$	81.03(81.27)	6.43(6.28)	3.78(3.79)
5	**7.10b**	Zn / HOAc	THF	reflux	12	**7.12**	73	156-157	$C_{25}H_{22}N_2O$	82.05(81.93)	6.05(6.06)	7.67(7.65)
6	**7.10c**	Zn / HOAc	THF	reflux	12	**7.13**	90	oil	$C_{20}H_{28}N_2S$	73.35(73.13)	8.77(8.60)	8.49(8.53)
7	**7.15a**	PhMgBr	toluene	reflux	3	**7.18**	91	oil	$C_{17}H_{23}N$	84.93(84.58)	9.82(9.61)	5.76(5.81)
8	**7.17**	K_2CO_3	DMF	120	12	**7.20**	57	oil	$C_{19}H_{25}NO$	80.68(80.51)	9.11(8.90)	4.87(4.94)
9	**7.17**	$NaCH(COOEt)_2$	DMF	140	12	**7.21**	76	oil	$C_{26}H_{37}NS$	70.05(70.40)	8.51(8.41)	3.40(3.16)
10	**7.19**	NaCN	DMF	reflux	12	**7.22**	54[a]	oil	$C_{19}H_{22}N_2$	81.65(81.96)	8.12(7.97)	10.20(10.07)

[a] Yield was based on compound **7.15**.

CHAPTER VIII
CONCLUSION

1-Propargylbenzotriazole has been prepared and used in the syntheses of a wide range of heterocycles by [3 + 2] annulation including furans, dihydrofurans, pyrroles and indoles. The elaborations of benzotriazolylmethyl side chains attached to furan, pyrrole and indole rings by electrophilic as well as nucleophilic substitutions provided various substituted heterocycles. Therefore, 1-propargylbenzotriazole has been shown to be a useful synthetic building block for the syntheses of heterocycles.

BIBLIOGRAPHY

The references of each chapter are given at the end of each chapter. The reference system used here is that from the book series "Comprehensive Heterocyclic Chemistry", edited by Alan R. Katritzky and Charles W. Rees, Pergamon Press, Oxford, 1984. Throughout this proposal, references are designated a number-letter coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a references is quoted.

Some commonly used additional notes are given below:

1. The list of reference is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volumn number if relevant, (e) page number.
2. In the reference list the code is followed by the complete literature citation in the conventional manner.
3. For journals which are published in separate parts, the part letter of number is given (when necessary) in parentheses immediately after the journal code letters.
4. Journal column numbers are not included in the code numbers unless more than one volumn was published in the year in question, in which case the

volumn number is included in parentheses immediately after the journal code letters.

5. Parents are assigned appropriate three letter codes.

6. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter "B-".

7. Less common journals and books are given the code "MI" for miscellaneous.

8. Where journals have changed names, the same code is used throughout.

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BIOGRAPHICAL SKETCH

Jianqing Li was born in May, 1962, in Zhejiang Province, P. R., China. He received a B.S. degree in chemistry from Hangzhou University in July, 1985, and a M.S. degree in organic chemistry from the same university in July, 1988. From July, 1988, to July, 1990, he worked at Zhejiang Applied Chemistry Institute as an engineer. From July, 1990 to August, 1992, he worked with Professor Katritzky as a visiting scholar in the Chemistry Department of the University of Florida.

He started the Ph.D. program in the Chemistry Department of the University of Florida in August, 1992, under the supervision of Professor Katritzky.

He is married to Linghong Xie who is now a postdoctoral fellow in the Katritzky research group. They have a one-year-old daughter, Stephanie, who was born in Gainesville.

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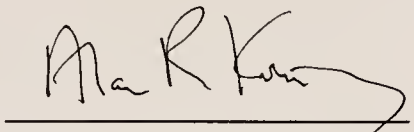

Alan R. Katritzky, Chair
Kenan Professor of Chemistry

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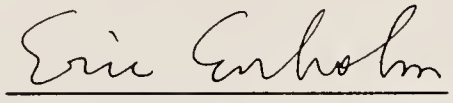

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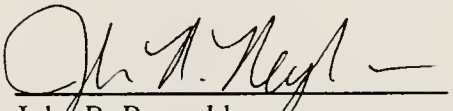

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Associate Professor of Chemistry

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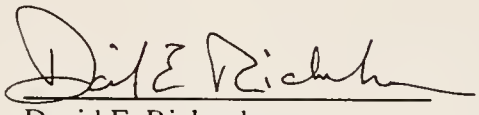

David E. Richardson
Professor of Chemistry

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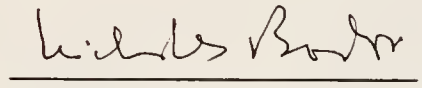

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 1995

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